VOL. XLV. MAY, 1911. NO. 5.

AMERICAN CHEMICAL JOURNAL

THE ACTION OF LIGHT ON ESTERS OF α-CYANCINNAMYLIDENACETIC ACID.

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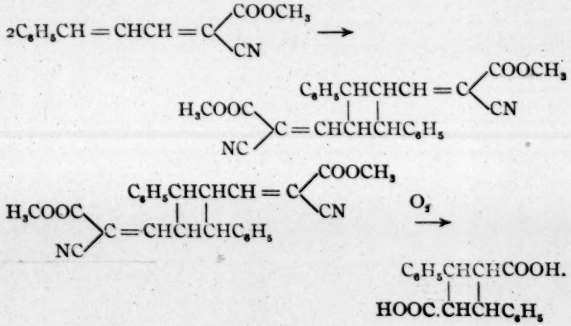
While carrying out reactions between cinnamylidene esters and Grignard's reagent, it was noticed that these esters are very sensitive to light. A bottle containing crystals of ethyl α-phenylcinnamylidenacetate, for example, which had been standing on a laboratory shelf for several months, was found to be coated with a pasty product smelling strongly of benzaldehyde. A sample of ethyl cinnamylidenacetate which had been standing a year was found to have changed entirely to a pasty substance which smelled of benzaldehyde. In the case of ethyl α-methylcinnamylidenacetate this decomposition is so rapid that the ester must be kept carefully protected from the light and purified immediately before it is used. Esters of cinnamylidenemalonic acid change more slowly, a decolorization taking place at the same time. With esters of α-cyancinnamylidenacetic acid this decolorization is the main reaction, little or no pasty product being formed. All of these changes are more rapid in direct sunlight.

In view of the important results obtained by the study of the action of light on organic compounds, it seemed of interest to investigate this reaction on a series of these esters. These experiments are now being carried on in this laboratory. The present paper deals only with results obtained in the study of the action of light on esters of α-cyancinnamyl-

idenacetic acid which was chosen as the member of the series having the most negative group in the α-position.

The reaction of light on a few cinnamylidene compounds has been investigated. Cinnamylidenemalonic acid loses color rapidly in the sunlight with the formation of a tetramethylene derivative,[1] a reaction analogous to that of cinnamic acid under the same conditions.[2] α-Methylcinnamylidenacetic acid also polymerizes to form a colorless tetramethylene compound[3] similar in structure to that obtained from the malonic acid.

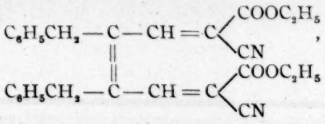
For the study of this reaction on esters of α-cyancinnamylidenacetic acid the methyl and ethyl esters were chosen. The reaction of the methyl ester in the sunlight has been found to be exactly analogous to that of the cinnamylidene acids previously investigated. The colorless product obtained by exposure of this compound is dimethyl diphenyltetramethylenebismethylenecyanacetate, the structure being proved by the fact that the product of oxidation is α-truxillic acid:



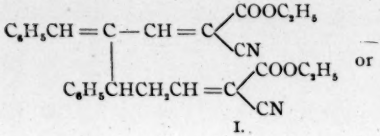
The behavior of the ethyl ester on exposure is, unexpectedly, quite different from that of the methyl compound. The first reaction is one of decomposition. The mass becomes

[1] Riiber: Ber. d. chem. Ges., **38**, 2411.
[2] Riiber; *Ibid.*, **38**, 2908.
[3] Macleod: This Journal, **44**, 331.

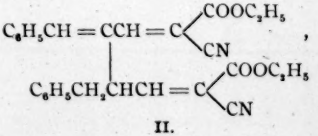
slightly sticky and smells of benzaldehyde. This reaction is accompanied by a decolorization, the speed of which is greater than that of the decomposition, as the quantity of pasty product does not increase appreciably after 8–10 hours, while the yellow color of the ester gradually disappears. After exposure, the colorless product, separated from oil and unchanged ester, was found to be a dimeric form of the original substance. It has not, however, the same structure as the compound obtained from the methyl ester. On oxidation it gives benzaldehyde and no trace of any truxillic acid, showing that the group $C_6H_5CH=$ is present and that there is no tetramethylene ring. For the structure of such a compound there are a number of possibilities. It is scarcely to be expected that an addition of the molecules would take place at the 1,2 double linkage because of the negative character of the groups attached to the α-carbon atom. If the addition is at the 3,4 double linkage, in order that one $C_6H_5CH=$ group be present in the dimolecular product there can be but a single carbon linkage between the molecules. Such a formula as



for example, could not be possible. Formulas which more nearly express the reactions of the compound are

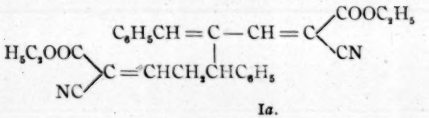


I.



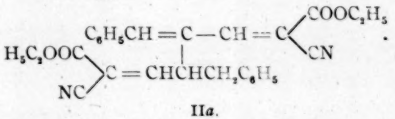
II.

or a more stable configuration might be



or

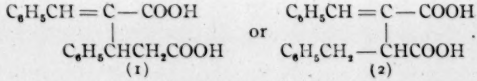
Ia.



IIa.

A closing of a ring through nitrogen is also not impossible, though none of the reactions of the compound point to such a structure.

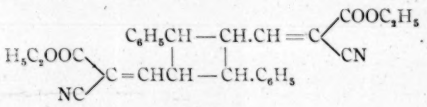
Results obtained by oxidation of this polymeric compound make probable the structures I or II, but do not make it possible to decide between them. The reaction of bromine on the esters, however, points strongly to formula I and to the configuration expressed by I*a*. Results are as follows: Oxidation of the polymeric ester with potassium dichromate gives as product an acid with the composition of a truxillic acid which contains, however, the group $C_6H_5CH=$, as it immediately decolorizes an alkaline solution of permanganate in a freezing mixture with formation of benzaldehyde. For such a compound there are possible the formulas



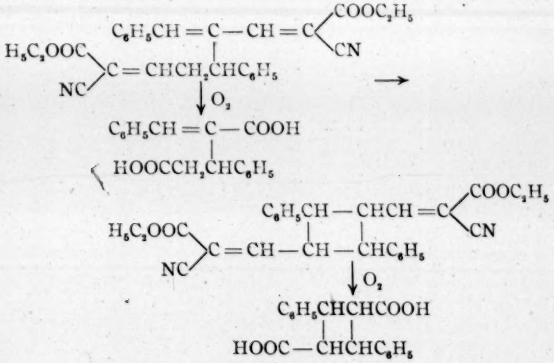
Oxidation of esters (I) and (II), respectively, would yield compounds having such constitution. Potassium permanganate oxidizes the substance to benzoic acid and an acid of the composition $C_{11}H_{10}O_5$, which might be obtained from (1) or (2). It has not, as yet, been possible to determine the structure of this compound.

By the action of bromine on a solution of the polymeric ester, which melts at 166°, this ester was transformed into

an isomer melting at 128°. This latter compound is exactly analogous in behavior to that obtained by the action of light on methyl α-cyancinnamylidenacetate. It has been proved to be ethyl diphenyltetramethylenebismethylenecyanacetate,



The formation of this compound from the higher melting polymeric ester makes most probable formula (I) advanced for that ester and, preferably, the configuration (I*a*). Isomerization of this compound to a tetramethylene derivative would involve the shifting of one hydrogen atom and closing of the tetramethylene ring. From a compound of formula (II), on the other hand, such a transformation would necessitate the breaking of a bond between carbon atoms and the subsequent closing of the tetramethylene ring. Formula (I*a*) is therefore to be preferred for the polymeric ethyl ester formed by exposure of the monomolecular ester to the light and, consequently, formula (1) for the acid obtained by oxidation of this ester:



It seemed scarcely probable that the difference in the reaction of methyl and ethyl α-cyancinnamylidenacetates in the light was due to the different chemical effect in the molecule of the methyl and ethyl groups. A more plausible explanation would seem to be that the two esters differ in configuration, one form being more stable for the methyl, the other for the ethyl ester. By the usual methods of preparation, only one form of each ester was obtained. Attempts to prepare a second ethyl ester from the methyl compound were, however, successful. Unstable ethyl α-cyancinnamylidenacetate was prepared by the action of potassium ethylate on the methyl ester in absolute ethyl alcohol solution.[1] This compound has, without doubt, the same configuration as the methyl ester from which it was formed, as its behavior is exactly analogous. On exposure to the light it loses color rapidly. The colorless product is diethyl diphenyltetramethylenebismethylenecyanacetate, melting at 128°, identical with the compound formed by isomerization, under the influence of bromine, of the high-melting dimeric ethyl ester. This new ethyl ester is unstable and changes over into the stable form on melting.

The transformations of these esters are, therefore, as shown in the scheme on the opposite page.

EXPERIMENTAL.

Action of Light on Methyl α-Cyancinnamylidenacetate.—α-Cyancinnamylidenacetic acid was prepared by a modification of the method of Fiquet.[2] One hundred grams of sodium cyanacetate and 125 grams of cinnamic aldehyde were heated for 45 minutes to a temperature of 180°. The reaction product was dissolved in the smallest possible quantity of boiling water, from which, on cooling, the sodium salt of α-cyancinnamylidenacetic acid separated in bright yellow, glistening plates. The acid obtained from this salt was pure after one crystallization from alcohol. The methyl ester was prepared by the method of Fiquet.[3] The ester may be prepared even

[1] Cf. Pfannl: Monats. Chem., **31**, 301.
[2] Ann. Chim. Phys., [6] **29**, 492.
[3] *Loc. cit.*

KOC2H5
C6H5CH=CHCH=C(CN)COOC2H5 (unstable)
C6H5CH=CHCH=C(CN)COOC2H5 (stable)
on melting
light
C6H5CH=CHCH=C(CN)COOC2H5
light
H5C2OOC
NC
C=CHCH(C6H5)CHC6H5
Br2
C6H5CH=C(CN)COOC2H5
C6H5CH=CH—CH=C(CN)COOC2H5
C6H5CH—CH—CH=C(CN)COOC2H5
C6H5CH—CHCH=C(CN)COOC2H5

more readily by condensation of methyl cyanacetate with cinnamic aldehyde in the presence of sodium methylate according to the directions of Bechert[1] for the ethyl ester. The ester, after several recrystallizations from methyl alcohol, melts sharply at 145°.

Molecular weight determined in boiling benzene ($K = 26.1$):

Grams solvent.	Gram substance.	Rise in boiling point.	Molecular weight.
48.95	0.5693	0.142	215
48.95	0.9184	0.226	217
	Calculated for $C_{13}H_{11}O_2N$,		213

In diffused daylight the ester loses its yellow color slowly. In the sunlight it crumbles rapidly to a white powder. In order to obtain this colorless product in quantity, the ester was finely powdered, spread out in a thin layer on plates of glass and exposed to the direct sunlight. As it was not possible in this way to determine the speed of reaction compared with that of other cinnamylidene esters because of the varying intensity of the sunlight, a mercury-vapor lamp was used for this purpose. Ten grams of ester were spread out as evenly as possible over glass plates twelve inches square and placed at an average distance of 24 cm. from the source of light. This was a Cooper Hewitt lamp of the tubular type, 67.5 cm. long, carrying a current of 3.2 amperes. The whole was protected from the sunlight by a covering of black cloth lined with white. The ester was stirred and spread out again every four hours. The temperature was 35° during exposure. In later experiments a tube of uviol glass was used, but the speed of reaction was not appreciably increased.

After exposure for 30 hours, 94 per cent. of the ester was found to have been decolorized. The product was washed thoroughly with ether and then with cold alcohol to rid it of small quantities of unchanged yellow ester. Even after much longer exposure there was always a trace of yellow ester left, probably because it had been protected from the light by the colorless product. The latter was purified by dissolving it in the smallest possible quantity of boiling ace-

[1] J. prakt. Chem., [2] **60**, 14.

tone and adding an equal volume of low-boiling ligroin. It separates in clumps of hard, clear crystals, melting at 172°.5. The compound is readily soluble in benzene chloroform and acetone; very slightly soluble in hot ether and alcohol; insoluble in ligroin.

Analysis:

0.1847 gram substance gave 0.4982 gram CO_2 and 0.0865 gram H_2O.

	Calculated for $C_{26}H_{22}O_4N_2$	Found.
C	73.24	73.56
H	5.16	5.20

Molecular weight determined in boiling benzene ($K = 26.1$):

Grams solvent.	Gram substance.	Rise in boiling point.	Molecular weight.
51.06	0.6703	0°.038	426
51.06	0.9040	0°.107	431

Calculated for $C_{26}H_{22}O_4N_2$, 426

The compound is, therefore, a dimeric form of the original ester.

The structure of this compound was determined by oxidation. Ten grams were dissolved in one liter of acetone and finely powdered potassium permanganate added slowly as long as decolorization took place. The solution was cooled by running water during oxidation. As soon as the permanganate was no longer decolorized rapidly the excess was decomposed by sulphur dioxide and the solution filtered. The oxides of manganese were washed with acetone and then extracted repeatedly with hot water. The aqueous solution deposited, when acidified, an acid which was purified by crystallization from methyl alcohol. It separated in clear prisms, which rapidly became opaque on exposure to the air and melted at 274°.

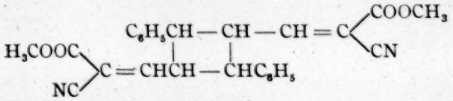
Analysis:

0.1765 gram substance gave 0.4741 gram CO_2 and 0.090 gram H_2O.

	Calculated for $C_{18}H_{16}O_4$.	Found.
C	72.97	73.25
H	5.40	5.69

The analysis and properties point to α-truxillic acid. That it was α-truxillic acid was shown by melting it with a sample of that acid obtained from another source. The mixture melted sharply at 274°. From the aqueous filtrate were obtained benzoic and oxalic acids.

The formation of these products on oxidation shows the dimeric ester to be dimethyl diphenyl-α-cyancinnamylidenacetate,



The solution of the compound in concentrated sulphuric acid has a bright lemon-yellow color. When this solution is poured into water the colorless compound is precipitated unchanged. When distilled, under 20 mm. pressure, the ester is depolymerized. The distillate solidifies in the receiver and, after one crystallization, melts sharply at 145°. This is analogous to the behavior of the polymeric products obtained by exposure of cinnamylidenmalonic and -methylacetic acids.

All attempts to saponify the ester in order to gain the corresponding tetramethylene acid gave only the monomolecular α-cyancinnamylidenacetic acid. This tetramethylene ring is, therefore, more easily broken down than that in the ester of diphenyltetramethylenebismethylenepropionic acid,[1] as the latter is saponified to the corresponding dimeric acid by boiling with aqueous potash.

Bromine reacts on the compound only to a very slight degree. Five grams of ester were dissolved in chloroform, 3.7 grams (1 mol.) of bromine added and the solution allowed to stand at 0° for two weeks. After this length of time there was no apparent change in the color of the solution. The solvent was allowed to evaporate spontaneously. The white crystalline product which separated was shown to be unchanged ester. Over 80 per cent. was regained. A very

[1] Macleod: *Loc. cit.*

small quantity of a volatile bromine compound was also formed, but not in sufficient quantity for investigation. This was probably formed by substitution. These results were to be expected from a compound of the structure of this ester, as the negative groups attached to the α-carbon atom would interfere with the addition of bromine to the α,β double linkage.

Action of Light on Ethyl α-Cyancinnamylidenacetate.—The ethyl ester was prepared by the method of Bechert.[1]

Molecular weight determined in boiling benzene ($K = 26.1$):

Grams solvent.	Grams substance.	Rise in boiling point.	Molecular weight.
48.51	0.3064	0°.073	228
48.51	1.0167	0°.247	221

Calculated for $C_{14}H_{13}O_2N$, 227

On exposure to the light the ester became a little pasty and the odor of benzaldehyde was evident. The color disappeared but slowly. Under exactly the same conditions of exposure as were used for the methyl ester, a 53 per cent. yield of colorless product was obtained after 60 hours. The amount of decomposition product was small, but evidently sufficient to protect much of the ester from the action of the light so that no amount of stirring was sufficient to expose all parts. As the decomposition reaction is evidently analogous to that of other cinnamylidene esters under investigation in which much larger amounts of pasty products are formed, the study of the small quantity obtained from the ester under consideration has been deferred until these other products have been investigated.

The reaction product was treated with alcohol at 40° to separate the colorless compound from unchanged ester and oily products. The pure white powder left was crystallized from boiling alcohol. It separates in clumps of branching white crystals melting at 166°. It is readily soluble in chloroform, acetone and benzene; slightly soluble in alcohol, boiling ligroin and ether.

Analysis:

[1] *Loc. cit.*

0.1749 gram substance gave 0.4729 gram CO_2 and 0.0949 gram H_2O.

	Calculated for $C_{28}H_{26}O_4N_2$.	Found.
C	74.00	73.74
H	5.72	6.02

Molecular weight determined in boiling benzene ($K = 261$):

Grams solvent.	Gram substance.	Rise in boiling point.	Molecular weight.
52.24	0.2936	0°.033	444
52.24	0.4286	0°.051	417
52.24	0.8970	0°.108	415

Calculated for $C_{28}H_{26}O_4N_2$, 454

The compound is a dimeric form of ethyl cyancinnamylidenacetate. It is not, however, analogous to that obtained from the corresponding methyl ester. It is much less stable than the latter and its reactions show it to be structurally different.

The compound decomposes slowly on boiling with alcohol, the solution becoming yellow. It dissolves readily in concentrated sulphuric acid. This solution, of a brilliant crimson color, when poured into water deposits a bright yellow solid which is a mixture of products from which no pure substance has been obtained. A complicated decomposition takes place on saponification. When distilled under diminished pressure, the distillate was found to consist of a mixture of stable and unstable ethyl α-cyancinnamylidenacetates. It is probable that the first reaction is the rearrangement of the compound into its tetramethylene isomer, decomposition of this into the unstable ethyl ester, analogous to the behavior of the methyl compound, and change of part of the unstable to the stable ester.

Attempts to determine the structure of the compound by oxidation have, so far, been only partially successful. With a solution of potassium permanganate in the cold, benzaldehyde is formed. The compound contains, therefore, the group $C_6H_5CH=$. The final products of oxidation with permanganate were found to be benzoic acid and a trace of an acid melting at about 179°. The quantity of this acid obtained in repeated experiments was not enough for analysis. When

potassium dichromate in glacial acetic acid was used for the oxidation there was obtained, beside benzoic acid, a trace of another acid melting at 185°. A good yield of this latter compound was obtained when the reaction was carried out in 50 per cent. acetic acid. Two grams of the ester were added to 100 cc. of 50 per cent. acetic acid in which 5 grams of potassium dichromate were dissolved. The mixture was boiled for about 15 minutes until the ester had gone into solution. From the reaction mixture the solvent was allowed to evaporate at room temperature for 48 hours. The liquid was then found to be filled with yellow plate-like crystals. These were washed with water and recrystallized from dilute methyl alcohol. The compound was found to be an acid which, after repeated crystallizations, separates in fine white needles melting at 185°. At 260° evolution of a gas begins.

Analysis:

0.1559 gram substance gave 0.4181 gram CO_2 and 0.0801 gram H_2O.

	Calculated for $C_{13}H_{10}O_4$.	Found.
C	72.97	73.13
H	5.40	5.70

The acid is readily soluble in acetone, chloroform and alcohol; sparingly soluble in ether and benzene; insoluble in water.

The *methyl ester* was prepared by dissolving 5 grams of the acid in 100 cc. of methyl alcohol saturated with hydrochloric acid. The mixture was shaken vigorously until the acid was all in solution. The methyl ester began to crystallize out of solution almost immediately. A quantitative yield was obtained. The compound is readily soluble in hot methyl and ethyl alcohols and ether, very sparingly soluble in these solvents in the cold. It separates from methyl alcohol solution in clear rhombic crystals melting at 132°.

Analysis:

0.1736 gram substance gave 0.4708 gram CO_2 and 0.0973 gram H_2O.

	Calculated for $C_{13}H_{10}O_4(CH_3)_2$.	Found.
C	74.07	73.98
H	6.17	6.22

These results show that the acid is dibasic and that the two carboxyl groups are not attached to the same carbon atom, as the acid does not begin to decompose until heated 75° above its melting point. As an alkaline solution immediately decolorizes potassium permanganate in a freezing mixture with formation of benzaldehyde, the group $C_6H_5CH=$ is present.

It was very difficult to obtain pure products by the oxidation of this acid. After repeated failures the experiment was carried out as follows: Four and five-tenths grams of acid were dissolved in acetone which was kept cold in a freezing mixture and 5.5 grams of potassium permanganate were added during the course of one hour. The excess of oxidizing agent was then decolorized with sulphur dioxide and the oxides of manganese filtered. The acetone was allowed to evaporate spontaneously from the filtrate. The oxides of manganese were dissolved with sulphur dioxide in dilute sulphuric acid and the solution extracted with ether. As the same products were obtained from the ether and acetone solutions and as they were not very soluble in ether, it was found best in subsequent experiments to make the acetone solution strongly acid with sulphur dioxide when the excess of permanganate was decolorized. After removal of the solvents by spontaneous evaporation, the residues were treated with hot water. The aqueous solution deposited, on cooling, a mass of fine white needles which were a mixture of benzoic acid and an acid melting at 179° with violent evolution of carbon dioxide. This mixture was carefully dried in the air and the acids separated by extraction with chloroform. From the chloroform solution a quantitative yield of benzoic acid was obtained. The residue, not soluble in chloroform, is an acid very soluble in ethyl and methyl alcohols, hot water and acetone, much less soluble in ligroin and ether. Repeated attempts to recrystallize the acid were unsuccessful. The only solvent from which it separates in a crystalline condition is hot water, which cannot be used successfully, however, as the acid loses carbon dioxide at the temperature at which solution takes place. This accounts for the small yield of

this acid obtained—28 per cent. of the calculated on the basis of structure (1) or (2). The residue from the chloroform extraction, which melts sharply at 179°, was therefore used in subsequent work.

Analysis of air-dried acid:

0.1505 gram substance gave 0.2938 gram CO_2 and 0.0743 gram H_2O.

	Calculated for $C_{11}H_{10}O_5$.	Calculated for $C_{11}H_{10}O_5.1.5H_2O$.	Found.
C	59.49	53.01	53.84
H	4.50	5.22	5.48

The acid was then allowed to stand over sulphuric acid in a desiccator; sample I for twelve days, sample II for six weeks.

I. 0.1553 gram substance gave 0.3232 gram CO_2 and 0.0715 gram H_2O.

II. 0.1603 gram substance gave 0.3363 gram CO_2 and 0.0715 gram H_2O.

	Calculated for $C_{11}H_{10}O_5.0.5H_2O$.	Found.	
		I.	II.
C	57.10	56.76	57.21
H	4.70	5.11	4.95

The composition of the acid agrees with that of an acid, $C_{11}H_{10}O_5$, containing 0.5 molecule of water of crystallization. The acid was shown to contain water of crystallization in the following way: A small quantity of sample II was mixed with an equal bulk of anhydrous cupric sulphate and heated in an oil bath. At 179° the acid melted to a clear liquid. Carbon dioxide was given off and, at the same time, the cupric sulphate became a brilliant blue. It was not found possible to drive off this water of crystallization below the temperature at which the acid loses carbon dioxide. Neither has it as yet been possible to purify the substance formed by loss of carbon dioxide from the acid. Attempts to oxidize this substance have given only oily products.

When the acid melting at 179° was treated with methyl alcohol saturated with hydrogen chloride an oil and a very small quantity of a crystalline ester were formed. The acid

undoubtedly loses carbon dioxide during esterification. Attempts to obtain this ester by oxidizing the ester of the acid melting at 185° were also unsuccessful. Under the conditions necessary for oxidation of the acid its ester is only partially oxidized, a considerable quantity being regained unchanged. The only products of oxidation are benzoic acid and an oil from which no pure substance has, as yet, been obtained.

There is, then, no proof of the structure of the acid melting at 179° and, therefore, from this work it is impossible to decide between formulas (1) and (2) advanced for the acid melting at 185° obtained by oxidation of the polymeric ethyl ester. An acid of either formula would be expected to give, on oxidation, the acid $C_{11}H_{16}O_5$.

Reaction of Bromine on the Polymeric Ester Melting at 166°.—A chloroform solution of 5 grams of ester was cooled in a freezing mixture and 3.5 grams of bromine in the same solvent added slowly. The color of the bromine solution disappeared gradually. The solution remained at 0° for one week and the solvent was allowed to evaporate spontaneously. The residue, a heavy yellow oil, was stirred with a small quantity of methyl alcohol, cooled to 0°. Gradually a white, granular solid separated. This was filtered, washed with cold alcohol and recrystallized from hot methyl alcohol. It separates in shining white crystals, melting at 126°–127°. It is very readily soluble in acetone, chloroform and benzene; slightly soluble in cold alcohol and ether. The analyses show the substance to be a dibrom addition product:

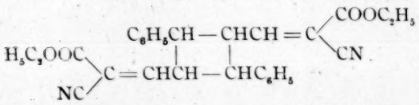
0.1619 gram substance gave 0.3206 gram CO_2 and 0.0711 gram H_2O.

	Calculated for $C_{20}H_{28}O_4N_2Br_2$.	Found.
C	54.72	54.03
H	4.23	4.87

The alcohol washings from this product contained a small quantity of a volatile bromine compound which attacked the eyes. When poured into water the solution deposited a pasty mass containing bromine from which no pure com-

pound could be obtained. The quantity of these secondary products was very small.

Isomerization of the Polymeric Ester (Melting at 166°) to Form Diethyl Diphenyltetramethylenebismethylenecyanacetate,



.—In one experiment for the preparation of the bromine compound just described, considerably less than the calculated quantity of bromine was used. The solution was treated exactly as before. A crystalline compound, which melted at 128°, separated from the methyl alcohol. This was found to contain no bromine and analyses showed it to be isomeric with the polymeric ester melting at 166°. The latter had, therefore, been transformed under the influence of bromine. The alcohol washings deposited a mixture of bromine compounds as before.

Diethyl diphenyltetramethylenebismethylenecyanacetate, melting at 128°, is readily soluble in benzene, chloroform, acetone and hot methyl and ethyl alcohols, slightly soluble in ether and ligroin. It may be purified by crystallization from alcohol, but better by solution in a small quantity of boiling benzene and addition of an equal volume of ligroin. From this it separates in small clumps of colorless compact crystals.

Analysis:

0.1509 gram substance gave 0.4101 gram CO_2 and 0.0800 gram H_2O.

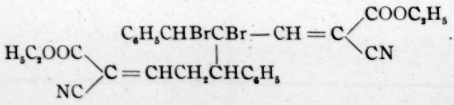
	Calculated for $C_{28}H_{26}O_4N_2$.	Found.
C	74.00	74.11
H	5.72	5.88

Molecular weight determined in boiling benzene ($K = 26.1$):

Grams solvent.	Gram substance.	Rise in boiling point.	Molecular weight.
33.08	0.1974	0°.035	446
	Calculated for $C_{28}H_{26}O_4N_2$,		454

The behavior of this compound is exactly like that of the polymeric methyl ester. It dissolves in concentrated sulphuric acid to a clear yellow solution from which water precipitates the colorless ester unchanged. On oxidation with potassium permanganate in acetone solution the products are α-truxillic, benzoic and oxalic acids. There can be, therefore, no doubt as to the structure of this compound.

The formation of this tetramethylene derivative from the high-melting polymeric ester by action of bromine makes most probable formula (Iα) proposed for the latter compound, as was pointed out in the introduction, and, consequently, the formula (1) for the acid obtained by its oxidation. The dibrom addition product would have, accordingly, the structure



It has not been possible to prepare again this tetramethylene derivative by this method. All attempts to duplicate the conditions of the reaction described have resulted in the formation of the bromine compound described above. The polymeric ester melting at 166° has been treated in chloroform and carbon tetrachloride solutions with bromine, iodine and hydrochloric acid in varying concentration, at 0°, at room temperature, in the dark and in the sunlight. In all cases the original ester or, with bromine, the dibrom addition product, have been the only substances isolated.

The compound has, however, been prepared by exposure to the light of the unstable ethyl α-cyancinnamylidenacetate.

Unstable Ethyl α-Cyancinnamylidenacetate.

Preparation.—The method used was that of Pfannl[1] for the mutual replacement of alkyl groups in esters of dibasic organic acids. This method was tried in order, if possible, to prepare from methyl cyancinnamylidenacetate an ethyl ester.

[1] *Loc. cit.*

This might be expected to have the same configuration as the methyl ester, since the reaction takes place at room temperature, and, if so, would be isomeric with the ethyl ester already known if the assumption as to the difference in the reaction of these two compounds in the light is correct.

Five grams of the methyl ester were suspended in 500 cc. absolute ethyl alcohol and the calculated quantity of potassium (0.9 gram) in ethyl alcohol solution added slowly. The mixture was shaken for about an hour and a half until the methyl ester was all in solution. Dilute sulphuric acid was added in quantity sufficient to neutralize the solution and the solvent allowed to evaporate spontaneously. After one-half the alcohol had evaporated the residue was poured into water, the solid separating filtered, dried and dissolved in hot absolute alcohol. An ester separated in yellow needles which were washed with cold alcohol and again crystallized.

Properties.—The ester separates from concentrated solution in compact branching clumps somewhat different in appearance from the needles of the usual form. It is so much less soluble in alcohol than the latter that the two forms may be separated by fractional crystallization from alcohol.

On exposure to the light the ester decolorizes rapidly. The colorless product, washed with alcohol, crystallized from boiling alcohol in small compact crystals, melting at 128°. When melted with diethyl diphenyltetramethylenebismethylenecyanacetate, which had been prepared by isomerization of the polymeric ethyl ester melting at 166°, the two were found to be identical. This reaction proves that the ester obtained by the Pfannl reaction is not identical but isomeric with the ethyl α-cyancinnamylidenacetate previously known.

Each of the two ethyl esters melts at 113° and a mixture of the two at the same temperature, indicating that the new ester is unstable and changes over into the stable, usual form at or below its melting point. This was shown by dividing a portion of the new ester into two parts. One portion, (*A*), was exposed to the light. The other, (*B*), was melted, the product recrystallized from alcohol and then exposed. From (*A*) was obtained the polymer melting at 128°; from (*B*) that

melting at 166°. The new ester is, therefore, the unstable form.

To distinguish between these isomeric esters, the best method is to expose small quantities of each to the light and compare the products formed. This can be done with extremely small amounts, as the polymers may be distinguished from each other in minute quantities by the reaction with concentrated sulphuric acid. The low-melting compound dissolves slowly in the acid. The solution is a clear yellow. The high-melting compound dissolves instantly to form a brilliant crimson solution.

The quantity of unstable ester obtained in this reaction was small. It is hoped that it may be possible to perfect the method so that larger yields of the substance may be obtained and studied further. It is possible that this method may be found to be of value for the preparation of other esters which are unstable, and, therefore, not obtained under the usual conditions of ester formation.

CHEMICAL LABORATORY,
BARNARD COLLEGE,
Feb., 1911.

[Contributions from the Sheffield Laboratory of Yale University.]

CXCI.—ALKYLATION OF AROMATIC AMINO ACIDS: 3-AMINO-2,4-DIMETHYLBENZOIC ACID.

BY HENRY L. WHEELER AND CHARLES HOFFMAN.

[FIFTH PAPER.]

Our previous papers on the alkylation of aromatic amino acids have been published in THIS JOURNAL.[1]

In regard to the methylaminobenzoic acids, we found that 2-amino-3-methylbenzoic acid (I), which is represented in Beilstein's *Handbuch*[2] as "4-Aminotoluylsäure" (2-amino-5-methylbenzoic acid), was readily alkylated when warmed with four molecular proportions of potassium hydroxide and five of alkyl halide in alcoholic solution.

The products with ethyl iodide were *N*-monoethylamino

[1] **42**, 455 (1909); **43**, 398 (1910); **44**, 113, 441 (1910).
[2] III, **2**, 1337.

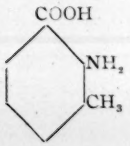
acid (15 parts), *N*-diethylamino acid (1 part) and a small amount of *O*-ester (2 parts). The alkylation therefore, in this case, took place for the greater part on the nitrogen.[1] The structure of this amino acid appears to have now been definitely settled as 2-amino-3-methylbenzoic acid ("2-Amino-*m*-toluylsäure") by Findeklee[2] and Müller.[3]

We may add, in confirmation of this, that the acid on distilling with calcium oxide gives *o*-toluidine. If the acid were 2-amino-5-methylbenzoic acid, as previously represented, it would yield *p*-toluidine by this treatment.

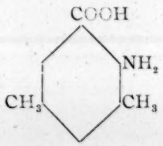
2-Amino-3,5-dimethylbenzoic acid (II) has an analogous structure to that of the above acid, inasmuch as the amino group is situated between the $—CH_3$ and —COOH groups, and on alkylation it behaves in a similar manner.[4]

With ethyl iodide and alkali the products were *N*-diethylamino acid (30 parts), *N*-monoethylamino acid (10 parts), a small amount of ester (1 part), and unaltered acid (5 parts).

4-Amino-3,5-dimethylbenzoic acid (III) reacted, under the same conditions, in an entirely different and abnormal manner on alkylation. In this case only the ethyl ester (42 per cent.) and unaltered acid was obtained.[5]



I.



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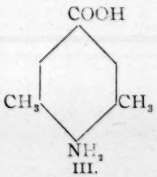


III.

With these results it was of interest to examine the behavior of the isomeric 3-amino-2,4-dimethylbenzoic acid (VIII), which, like the preceding acid (III), has the amino radical surrounded by methyl groups. This has now been done and

[1] THIS JOURNAL, **44,** 123 (1910).
[2] Ber. d. chem. Ges., **38,** 3553 (1905).
[3] *Ibid.*, **42,** 430 (1909).
[4] THIS JOURNAL, **44,** 121 (1910).
[5] *Ibid.*, **44,** 120 (1910).

we find that 3-amino-2,4-dimethylbenzoic acid reacts with both methyl and ethyl iodides like 4-amino-3,5-dimethylbenzoic acid, since it alkylates with difficulty and esters are the chief products. For example, with ethyl iodide we obtained the *O*-ester (4.5 parts), unaltered acid (5.5 parts), and a little of the *N*-monoethyl acid (1 part).

These results afford further evidence that methyl groups adjacent to an amino group interfere with the normal alkylation of this radical in amino acids, while the curious fact remains that a methyl group and a carboxyl in these positions permit the alkylation to take place normally with the formation of *N*-alkyl derivatives as the main products. The introduction of negative groups causes the *O*-esters to again predominate; 5-iod-2-amino-3-methylbenzoic acid[1] gives mainly the *O*-ester, the ratio of ester to *N*-alkyl acid being 15 : 4, while 2,4,6-tribrom-3-aminobenzoic acid yields exclusively the *O*-ester.

3-Amino-2,4-dimethylbenzoic acid is new. It was prepared as follows: 2,4-Dimethylbenzoic acid (IV) was nitrated and the resulting 3,5-dinitro-2,4-dimethylbenzoic acid (V) was reduced by means of ammoniom sulphide. This reagent reduced only the nitro group in the 5-position, giving 3-nitro-5-amino-2,4-dimethylbenzoic acid (VI). When this acid was diazotized and treated with alcohol the amino group was removed and 3-nitro-2,4-dimethylbenzoic acid (VII) was obtained. Then, on reducing with ferrous sulphate and ammonia, 3-amino-2,4-dimethylbenzoic acid (VIII) was formed. The yields were practically quantitative in each step except the preparation of 3-nitro-2,4-dimethylbenzoic acid, in which case the amount of material obtained was 70 per cent. of the calculated. The preparation of 3-nitro- and 3-aminoxylic acid by this method is therefore a simple matter.

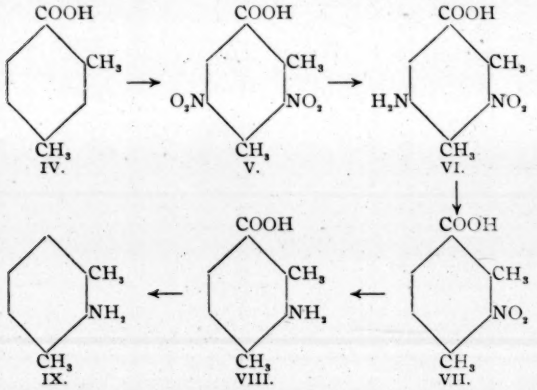
Claus[2] believed that he had obtained 3-nitro-2,4-dimethylbenzoic acid by oxidizing 3-nitro-2,4-dimethylphenylmethyl ketone, a by-product difficult to purify which was formed

[1] THIS JOURNAL, **44**, 116 (1910). Previously represented as 3-iod-2-amino-5-methylbenzoic acid.

[2] J. prakt. Chem., [2] **41**, 500 (1890).

in small amount in the nitration of 2,4-dimethylphenylmethyl ketone. The melting point he assigns to 3-nitroxylic acid (135°) is 44° lower than that of our acid.

The structure of our nitro and amino acids (VII and VIII) was shown on distilling the amino acid with calcium oxide, whereupon *vic.-m*-xylidine or 2-amino-1,3-xylene (IX) was obtained. This oil was identified by means of its acetyl derivative. The synthesis may be represented as follows:



Since the above reactions are smooth throughout, they might be employed for the preparation of *vic.-m*-xylidine free from isomers. This base is now usually obtained by separating it, in a number of ways, from the commercial mixture of xylidines in which it occurs in small amount (about 2.7 per cent.[1]).

EXPERIMENTAL PART.

3,5-Dinitro-2,4-dimethylbenzoic Acid.—This acid has been prepared by Frey and Horowitz,[2] who nitrated 2,4-dimethylbenzoic acid, using 10 parts of nitric acid (specific gravity

[1] Hodgkinson and Limpach: J. Chem. Soc., **77**, 67.
[2] J. prakt. Chem., [2] **43**, 120 (1891).

1.4) and 30 parts of concentrated sulphuric acid. They do not give the yield.

We found that the following procedure gave a yield of 95 per cent. of the calculated. 2,4-Dimethylbenzoic acid was prepared according to the method of Bouveault.[1] Seventy grams of xylene gave 60 grams of pure acid.

Thirty cc. of concentrated nitric acid (specific gravity 1.4) were mixed with 45 cc. of concentrated sulphuric acid and 15 grams of *m*-xylic acid were slowly added to this mixture at the temperature of the room. When all the acid was added a violent reaction took place, after which the mixture was heated for 3 hours on the steam bath. The crystalline product that separated, on pouring into water, was washed and dried; it weighed 23 grams and melted at 195°.

3-Nitro-5-amino-2,4-dimethylbenzoic Acid.—This new acid was prepared as follows: Twenty grams of the above dinitro acid were added to a mixture of 150 cc. of concentrated ammonium hydroxide and 100 cc. of alcohol. The mixture was saturated with hydrogen sulphide at ordinary temperature and then warmed on the water bath under a return condenser for a half hour. It was then cooled, saturated again with hydrogen sulphide and reheated an hour longer on the steam bath. The alcohol and excess of ammonia were evaporated and the filtered solution was precipitated with dilute hydrochloric acid, avoiding an excess since the amino acid is soluble in hydrochloric acid. It is not precipitated by acetic acid. The yield of crude product, which melted with decomposition at 240°, was 16.5 grams, or 95 per cent. of the calculated. It crystallized from alcohol in beautiful, straw-colored prisms which are difficultly soluble in water. Three crystallizations gave a product melting to a dark oil at 251°.

	Calculated for $C_9H_{10}O_4N_2$.	Found.
N	13.33	13.26

The *hydrochloride*, $C_9H_{10}O_4N_2.HCl$, was obtained on crystallizing the acid from dilute hydrochloric acid. It formed

[1] Bull. soc. chim., [3] **17**, 363.

clusters of large, spikelike prisms which melted at 250°, with effervescence.

	Calculated for $C_9H_{11}O_4N_2Cl$.	Found.
N	11.36	10.97

The *acetyl derivative* was formed by treating the amino acid with acetyl chloride. It is moderately soluble in water, readily in hot alcohol, and it crystallizes in colorless needles which melt to a dark oil at 247°. When mixed with unaltered acid the melting point was lowered to 200°.

	Calculated for $C_{11}H_{12}O_5N_2$.	Found.
N	11.11	11.00

3-Nitro-2,4-dimethylbenzoic Acid.—Fifteen grams of 3-nitro-5-amino-2,4-dimethylbenzoic acid were dissolved at 0° in 24 cc. of concentrated sulphuric acid, by grinding in a mortar, and fourteen grams of dry sodium nitrite were added. The thick, pasty mass which formed was poured upon crushed ice; this gave a yellow diazo solution. It was filtered into 200 cc. of boiling alcohol and the heating was continued until the dark red color which formed at first had practically disappeared. When the solution was poured upon crushed ice, 9 grams of crude acid, or 70 per cent. of the calculated, separated. This acid is difficultly soluble in hot water, readily in alcohol and only moderately soluble in benzene. It crystallizes from the latter solvent in pointed prisms having a light brown color and melting at 179°. Claus[1] describes this compound as melting at 135°.

	Calculated for $C_9H_9O_4N$.	Found.
N	7.18	7.17

The *amide*, $C_8H_8NO_2.CONH_2$, obtained by treating the acid with phosphorus pentachloride and then pouring the product upon solid ammonium carbonate, crystallized from water in plates and melted at 138°.

	Calculated for $C_9H_{10}O_3N_2$.	Found.
N	14.43	14.10

[1] *Loc. cit.*

3-Amino-2,4-dimethylbenzoic Acid.—Ten grams of 3-nitro-2,4-dimethylbenzoic acid were dissolved in 125 cc. of concentrated ammonium hydroxide and 125 grams of ferrous sulphate (calculated for 8 moles), dissolved in 200 cc. of water, were added. This mixture was then heated on the steam bath for one hour, after which it was filtered and the filtrate concentrated to a small volume. It was then acidified with dilute acetic acid and, on standing for some time, the separation of amino acid was complete. The yield of crude product was 7.5 grams or 93 per cent. of the calculated. When crystallized twice from water it formed needles or prisms, the crystalline form depending on the concentration, and it melted to a brown oil at 146°. Its solution in water or dilute alcohol shows a green fluorescence. It is readily soluble in ethyl acetate, alcohol and benzene.

	Calculated for $C_9H_{11}O_2N$.	Found. I.	II.
N	8.48	8.46	8.79

The *acetyl derivative*, $C_9H_9O_2NHCOCH_3$, was formed by treating the acid with acetic anhydride. It crystallized from alcohol in needles which melted with decomposition at 243°. It is moderately soluble in warm water and readily soluble in dilute alcohol.

	Calculated for $C_{11}H_{13}O_3N$.	Found.
N	6.76	6.93

vic.-m-*Xylidine* was obtained from 2,4-dimethyl-3-aminobenzoic acid when the acid was mixed with an equal weight of calcium oxide and the mixture distilled on the sand bath. The oil obtained was treated with an excess of acetic anhydride. Upon cooling, the crystalline substance that separated was crystallized twice from water. It melted at 175°. The melting point of 1,3-dimethyl-2-acetanilide (*vic.-m*-acetxylidide) is variously given from 174°–176°; that of 2,4-dimethylacetanilide at 129°; while the other theoretically possible dimethylacetanilide, namely 3,5-dimethylacetanilide, has been found, by different observers, to melt at 138°, 140°.5 and 144°.5.

	Calculated for $C_{10}H_{13}ON$.	Found.
N	8.59	8.45

3-Iod-2,4-dimethylbenzoic Acid.—Four and eight-tenths grams of the above amino acid, 25 cc. of sulphuric acid, and 4.3 grams of dry sodium nitrite (calculated for 2 moles) were mixed in the cold and poured upon crushed ice. The diazo solution was filtered into an excess of potassium iodide (30 grams) dissolved in water; on warming, and then treating the product with acid sodium sulphite, 6 grams, or 75 per cent. of the calculated, of crude iod acid was obtained. It crystallized from dilute alcohol in needlelike prisms which, after three crystallizations, melted at 167°. It is readily soluble in alcohol and benzene.

	Calculated for $C_9H_9O_2I$.	Found.
I	46.01	45.88

Ethylation of 3-Amino-2,4-dimethylbenzoic Acid.—Five grams of the acid, 7 grams of potassium hydroxide (4 moles) in alcoholic solution and 22 grams of ethyl iodide (5 moles) were mixed and the whole heated under a return condenser for 2 hours. The alcohol was then evaporated and the residue taken up in water. An oil remained which did not solidify on cooling in a freezing mixture. It was extracted with ether and the ether solution was shaken with dilute ammonium hydroxide. Upon evaporating the ether 1.8 grams of oil were obtained which did not crystallize. This proved to be the primary amino ester, since on boiling with alcoholic potassium hydroxide 3-amino-2,4-dimethylbenzoic acid was obtained. On evaporating the alcoholic solution, taking the residue up in water and precipitating with acetic acid, the precipitated acid melted at 146° and, when mixed with unaltered acid, the melting point was not changed.

The ammonia solution was evaporated to dryness and the residue extracted with ethyl acetate, which, upon evaporation, gave 0.4 gram of oil. This oil dissolved in dilute hydrochloric acid, and gave a precipitate when cooled to 0° and a few drops of dilute sodium nitrite were added.

The water solution from the first extraction was acidified with acetic acid, evaporated to dryness, and the residue was extracted with ethyl acetate, whereupon 2.2 grams of unaltered acid melting at 146° were obtained. When mixed with unaltered acid the melting point remained the same.

Methylation of 3-Amino-2,4-dimethylbenzoic Acid.—The proportions of acid, alkali and alkyl halide were the same as in the previous experiment. Methyl alcohol was used in place of ethyl alcohol, the other conditions being the same. On evaporating the alcohol an oil was again obtained in this case. This partially solidified on cooling. The residue was extracted with water and from this solution 3.2 grams of unaltered acid were recovered on acidifying with acetic acid.

The residue insoluble in water was extracted with dilute ammonia and ether. On evaporating the ether 0.7 gram of oil was obtained, which, on saponification, gave unaltered acid melting at 146°.

The ammonia solution was acidified with acetic acid, after evaporation, and one gram of substance was obtained which, on crystallizing from water, melted at 146°.

The mother liquor from this crystallization, on acidifying with hydrochloric acid, cooling to 0° and adding dilute sodium nitrite, gave a crystalline precipitate. This was filtered and washed with water to remove all the sodium nitrite. A small portion was added to a solution of diphenylamine in concentrated sulphuric acid. An intense blue color was immediately formed, showing the presence of a nitroso compound and therefore the formation of 3-methylamino-2,4-dimethylbenzoic acid in this alkylation.

Methylation of 2,4,6-Tribrom-3-aminobenzoic Acid.

Methyl 2,4,6-Tribrom-3-aminobenzoate.—Eight grams of the acid, 1.74 grams of potassium hydroxide (calculated for 1.5 moles) in 50 cc. of methyl alcohol and 12.1 grams of methyl iodide (2 moles) were mixed and warmed for 15 hours. On evaporating the alcohol and treating the residue with 100 cc. of water a gummy residue remained, which, on drying, weighed 3.2 grams. This was insoluble in alkali and on crystallizing

from alcohol, in which it is readily soluble, colorless needles melting at 93°–94° were obtained. A nitrogen determination agreed with the calculated for a methyl ester, and on saponifying with alcoholic potassium hydroxide the unaltered acid was obtained.

	Calculated for $C_8H_9O_2NBr_2$.	Found.
N	3.66	3.57

The aqueous solution or extract mentioned above, on acidifying with hydrochloric acid, gave 4.1 grams of unaltered acid melting at 168°–169°. In this experiment 38 per cent. of the acid was converted into ester.

In another experiment the same proportions were used, only the time of heating was shortened to 3 or 4 hours. This gave 17 per cent. of ester and 80 per cent. of unaltered acid was recovered.

o-Toluidine from 2-Amino-3-methylbenzoic Acid.—The base was obtained by distilling the acid with an equal weight of calcium oxide. The acid was obtained as follows: *m*-Toluic acid was nitrated and the chief product, melting at 219°–220°, was reduced with ferrous sulphate and ammonia. This gave the amino acid melting at 172°.

Since we also obtained the nitro acid melting at 211° in the nitration of *m*-toluic acid, and this material was shown to be the 4-nitro-3-methylbenzoic acid by converting it into the amide melting at 151°,[1] and since there are only two mononitro-*m*-toluic acids with the nitro group ortho to methyl, it follows that the amino acid used by us, and melting at 172°, was 2-amino-3-methylbenzoic acid.[2]

The *o*-toluidine obtained was converted into the acetyl derivative. It melted at 110° and a nitrogen determination gave 9.20 per cent. nitrogen while the calculated is 9.39 per cent.

NEW HAVEN, CONN.,
January, 1911.

[1] Beilstein and Kreusler: Ann. Chem. (Liebig), **144**, 168.
[2] Wheeler and Hoffman: THIS JOURNAL, **44**, 113 (1910).

[Contributions from the Sheffield Laboratory of Yale University.]

CXCII.—ON HYDANTOINS: ALDEHYDE CONDENSATION PRODUCTS OF PHENYLTHIOHYDANTOINS.

By Henry L. Wheeler and Charles A. Brautlecht.

[SECOND PAPER.]

We have shown in our first paper[1] that hydantoin condenses with aldehydes on warming with anhydrous sodium acetate in glacial acetic acid.

We found also that 1-phenylhydantoin reacts in the same manner, but we observed no condensation when 3-phenyl- or 1,3-diphenylhydantoin was employed.

Erlenmeyer had previously stated that phenylhydantoin does not condense with benzaldehyde when warmed with acetic anhydride and fused sodium acetate.[2]

The failure of two of these types of hydantoins to condense with aldehydes might seem to be due to the presence of a phenyl group in the 3-position, or in other words, to the absence of the grouping $C=N—CH_2—C=O$, and, if this were true, then it would be expected from analogy that the corresponding normal thiohydantoins would behave in a similar manner.

We have now investigated the tendency of 1-phenyl-2-thiohydantoin (I), 2-thio-3-phenylhydantoin (II) and 2-thio-1,3-diphenylhydantoin (III) to react with aldehydes and have made the curious observation that not only does 2-thio-1-phenylhydantoin condense apparently more readily than hydantoin or the corresponding *O*-derivative, but also that both of the other types of thiohydantoins, having phenyl groups in the 3-position, readily give condensation products.

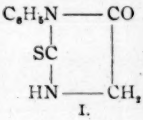
These results afford further evidence that the grouping $C=N—CH_2—C=O$ is not necessary to render the methylene hydrogen in hydantoins reactive towards aldehydes. This

[1] Wheeler and Hoffman: This Journal, **45**, 368.
[2] Ann. Chem. (Liebig), **307**, 73 (1899).

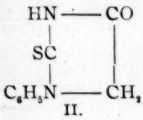
grouping has been discussed in this connection by Erlenmeyer, Junior,[1] although he found that creatine,

$$H_2N—C(:NH)—N(CH_3)CH_2COOH,$$

readily undergoes condensation with benzaldehyde.[2]



I.



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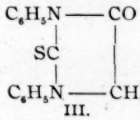


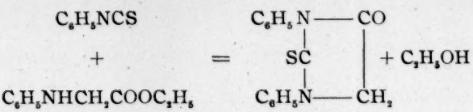
III.

2-Thio-1-phenylhydantoin (I) was prepared by combining glycine or its ethyl ester in alkaline solution with phenyl mustard oil.[3]

2-Thio-3-phenylhydantoin (II), which represents a new type of thiohydantoins, was prepared by warming the hydrochloric acid salt of phenylglycine ester with potassium thiocyanate; the resulting product, the thiohydantoic ester (IV), on warming with hydrochloric acid, gave the hydantoin.

IV.

2-Thio-1,3-diphenylhydantoin (III), another new type, was prepared by heating phenylglycine ethyl ester (or phenylglycine) with phenyl mustard oil.



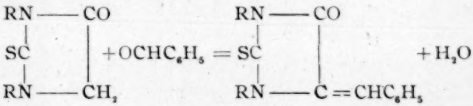
The condensation of hydantoins with aldehydes takes place with the separation of one molecular proportion of water, and since it makes no difference, in the case of thiohydantoins,

[1] Ann. Chem. (Liebig), **337**, 205 (1904).

[2] *Ibid.*, **284**, 49 (1895).

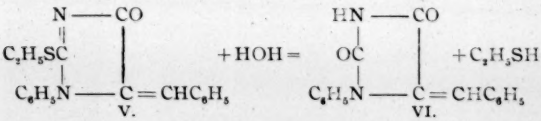
[3] Aschan: Ber. d. chem. Ges., **17**, 420 (1884). Marckwald, Neumark and Stelzner: *Ibid.*, **24**, 3278 (1891).

whether or not the hydrogen atoms attached to nitrogen are replaced by the phenyl group, it is evident that these hydrogen atoms take no part in the condensation. For example, the general reaction with benzaldehyde, in which R is either H or C_6H_5, is represented as follows:



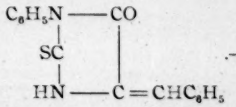
We intend to give a description of the chemical behavior of the aldehyde condensation products of thiohydantoins in later papers. It may be stated here, however, that both 2-thio-1-phenyl- and 2-thio-3-phenylhydantoins give 2-mercapto derivatives when warmed with alkali and alkyl halide. 2-Ethylmercapto-1-phenylanisalhydantoin, on boiling with hydrochloric acid, gives off mercaptan and yields 1-phenylanisalhydantoin. The product is identical with that resulting from the condensation of anisaldehyde with 1-phenylhydantoin.

When 2-ethylmercapto-3-phenylbenzalhydantoin (V) was boiled with hydrochloric acid it was likewise desulphurized and 3-phenylbenzalhydantoin (VI), which was not obtained by direct condensation, was formed:



EXPERIMENTAL PART.

2-Thio-1-phenylbenzalhydantoin,



.—In these condensations we have taken 1 part of phenylthiohydantion, 2 parts of fused sodium acetate and a little over the cal-

culated amount for 1 molecular proportion of aldehyde, the excess being from one-seventh to one-tenth of the calculated. The mixture was dissolved in 14 parts of glacial acetic acid and boiled from 1–2 hours. The addition of acetic anhydride was neither necessary nor advisable. In this case, from 10 grams of thio-1-phenylhydantoin with benzaldehyde, after heating for a short time, some of the condensation product separated from the hot solution. On cooling, water was added and the precipitated crude material was washed with water. When dry it weighed 14.6 grams, or the theoretical amount.

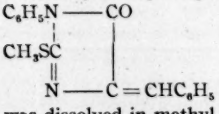
2-Thio-1-phenylbenzalhydantoin crystallized from alcohol in the form of yellow prisms, which melted to a clear oil at 204°. It was soluble in about 60 parts of boiling alcohol, practically insoluble in cold water but readily soluble in alkali with orange-yellow color. If dissolved in alkali without warming, and acetic acid or hydrochloric acid precipitated the unaltered hydantoin melting at 204°. When it was boiled for a few minutes in normal potassium hydroxide and then precipitated with hydrochloric acid at 0°, some hydrogen sulphide was noticed and a salmon-colored precipitate resulted. This melted with effervescence at 186°–188°. When this material was recrystallized from alcohol the hydantoin melting at 204° was obtained. The precipitate was therefore in all probability thiophenylbenzalhydantoic acid,

$$C_6H_5NHCSNHC(:CHC_6H_5)COOH.$$

The thiophenylbenzalhydantoin was crystallized twice from alcohol and dried at 110° for analysis:

	Calculated for $C_{16}H_{12}ON_2S$.	Found.
N	10.00	10.07

2-Methylmercapto-1-phenylbenzalhydantoin,



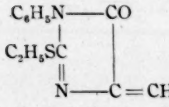
.—2-Thio-1-phenylbenzalhydantoin

was dissolved in methyl alcohol containing one molecular pro-

portion of sodium methylate and 1.5 times the calculated amount of methyl iodide was added. The reaction took place at ordinary temperature, the solution became deep ruby-red, and in a few minutes cream-colored, needlelike prisms separated, which on standing in the mother liquor for a few hours changed into compact octahedral blocks or pyramids. Both forms melted to a clear oil at 150° and when mixed the melting point was not altered. The change in form was only observed in the reaction mixture and not on crystallizing from ethyl or methyl alcohol. The yield of crude material, after evaporating the alcohol and washing with water, was quantitative.

	Calculated for $C_{17}H_{14}ON_2S$.	Found.
N	9.52	9.49

2-Ethylmercapto-1-phenylbenzalhydantoin,



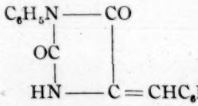
.—The solution of 2-thio-1-phenylbenzalhydantoin in alcohol containing one molecular proportion of sodium ethylate and two of ethyl bromide was warmed for a short time, or until it became neutral. On cooling, the material that separated was washed with water and recrystallized from alcohol. It formed straw-yellow needles, which melted to a clear oil at 123°.

	Calculated for $C_{18}H_{16}ON_2S$.	Found.
N	9.09	9.01

2-Benzylmercapto-1-phenylbenzalhydantoin was obtained by shaking the thiohydantoin in 20 per cent. potassium hydroxide solution with benzyl chloride. After washing with water and crystallizing from alcohol it gave almost colorless needles, melting to a clear oil at 178°–179°. Like the above methyl and ethylmercapto derivatives this substance was practically insoluble in water and cold dilute sodium hydroxide. It dis-

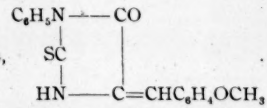
solved in about 890 parts alcohol at 22° and in about 137 parts of boiling alcohol.

	Calculated for $C_{23}H_{18}ON_2S$.	Found.
N	7.57	7.53



1-Phenylbenzalhydantoin, .—When the above mercapto derivatives are boiled with concentrated hydrochloric acid diluted with alcohol, mercaptan is evolved practically quantitatively. The phenylbenzalhydantoin crystallizes from alcohol in pale, cream-colored, twinned prisms or diamond-shaped blocks which melt to a clear oil at 243°.

	Calculated for $C_{16}H_{12}O_2N_2$.	Found.
N	10.61	10.57



2-Thio-1-phenylanisalhydantoin, —This was prepared from anisaldehyde and thio-1-phenylhydantoin; the yield was almost quantitative. It is practically insoluble in cold water and difficultly soluble in benzene. It is readily soluble in hot glacial acetic acid. It dissolves in about 124 parts of boiling alcohol and on cooling crystallizes in long, lemon-yellow needles melting at 214°.

	Calculated for $C_{17}H_{14}O_2N_2S$.	Found.
N	9.03	8.97

This hydantoin dissolves in dilute sodium hydroxide and gives a yellow, difficultly soluble sodium salt which crystallizes in plates and melts with decomposition at about 280°.

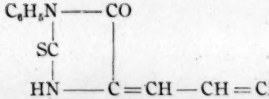
2-Ethylmercapto-1-phenylanisalhydantoin, from the above, sodium ethylate and an excess of ethyl bromide, formed

canary-yellow needles melting at 138°–139°, when crystallized from about 25 parts of alcohol.

	Calculated for $C_{19}H_{18}O_2N_2S$.	Found.
N	8.28	8.16

When this mercapto derivative was desulphurized by boiling with concentrated hydrochloric acid and alcohol, ethyl mercaptan was evolved and a quantitative yield of 1-phenyl-anisalhydantoin was obtained. This melted at 151°–152°[1] and proved to be identical with the product obtained by condensing hydantoin and anisaldehyde.

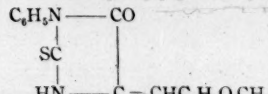
2-Thio-1-phenylcinnamylhydantoin,



, was obtained from thio-1-phenylhydantoin and cinnamaldehyde. The yield of crude product was 93.6 per cent. of the calculated. When crystallized from alcohol or glacial acetic acid it formed long, orange-colored, flat prisms melting to a dark brown oil at 272°–273°. It is practically insoluble in water and one part dissolves in about 305 parts of boiling alcohol. It is insoluble in ether and difficultly soluble in benzene. It is insoluble in dilute acids, but dissolves in concentrated sulphuric acid, giving an intense red color, and is precipitated unaltered from this solution on adding water.

	Calculated for $C_{18}H_{14}ON_2S$.	Found.
N	9.15	9.09

2-Thio-1-phenylpiperonalhydantoin,



, from thio-1-phenylhydantoin and piperonaldehyde, formed yellow plates melting at 222°–

[1] Wheeler and Hoffman: THIS JOURNAL, **45**, 368.

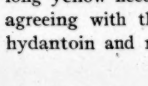
223°. It was crystallized from 28 parts of glacial acetic acid and then from hot alcohol in which it is more difficultly soluble. The yield of crude product that separated directly on adding water after condensation was 84 per cent. of the calculated, while more was obtained from the acetic acid filtrate on evaporating and treating the residue with water.

	Calculated for $C_{17}H_{12}O_3N_2S$.	Found.
N	8.64	8.64

When this hydantoin was dissolved in 20 parts of warm normal potassium hydroxide and the solution cooled, beautiful long yellow needles separated which gave results on analysis agreeing with those calculated for a potassium salt of the hydantoin and not for the hydantoic acid.

	Calculated for $C_{17}H_{11}O_3N_2SK$.	Found.
K	10.77	10.59

2-Thio-1-phenyl-p-nitrobenzalhydantoin,

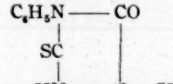


.—The condensation of *p*-nitrobenzaldehyde with thio-1-phenylhydantoin gave a very difficultly soluble product. For analysis it was crystallized from glacial acetic acid, then washed with alcohol and dried at 100°. It formed lemon-yellow, flat, pointed prisms which melted at about 278°–279°.

	Calculated for $C_{18}H_{11}O_3N_3S$.	Found.
N	12.92	12.90

This hydantoin is difficultly soluble in an excess of sodium hydroxide, owing to the formation of a rather insoluble sodium salt. It may be precipitated unaltered from its solution by hydrochloric acid.

2-Thio-1-phenylsalicylhydantoin,

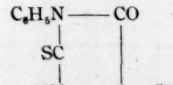


, formed straw-yellow prisms melting at 224°–225°, when crystallized from glacial acetic acid and alcohol.

	Calculated for $C_{16}H_{12}O_3N_2S$.	Found.
N	9.45	9.51

Thio-1-phenylsalicylhydantoin dissolved in sodium hydroxide, forming an intense orange-red solution, and hydrochloric acid reprecipitated the unaltered hydantoin. It is practically insoluble in ether and water and difficultly soluble in alcohol.

2-Thio-1-phenylfurfuralhydantoin,



.—The condensation product of furfuraldehyde with thio-1-phenylhydantoin formed yellow prismatic blocks, melting at 233°–234°, when crystallized from glacial acetic acid. It is difficultly soluble in alcohol and it dissolves in concentrated sulphuric acid, forming a yellow solution which changes to a dark green.

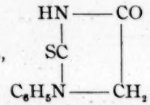
	Calculated for $C_{14}H_{10}O_3N_2S$.	Found.
N	10.37	10.40

Ethyl Phenylaminoacetate Hydrochloride, $HCl.C_6H_5NHCH_2COOC_2H_5$.—This salt, which appears to be new, was prepared by dissolving phenylglycine ester in dry ether and then saturating the solution with dry hydrogen chloride. The solution became warm and an oily precipitate first separated which soon changed to a white crystalline mass. This was washed with ether and dried over potassium hydroxide in a vacuum desiccator. It could be crystallized

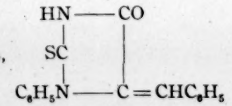
by dissolving in absolute alcohol and precipitating with ether. It then formed colorless plates which melted at about 119°.

	Calculated for $C_{10}H_{11}O_2NCl$.	Found.
Cl	16.47	16.32

On standing or on warming the salt turns green and decomposes.

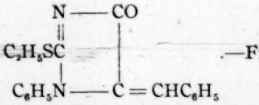
2-Thio-3-phenylhydantoin,  .—The above salt was dissolved in absolute alcohol containing a slight excess over the calculated of potassium thiocyanate and the solution boiled for about 4 hours. On evaporating the solution an oil was obtained in addition to potassium chloride and the excess of potassium thiocyanate. This residue was heated for two hours longer on the steam bath, then dissolved in alcohol and warmed with a little dilute hydrochloric acid. On evaporating the alcohol, crystalline material was obtained. This crystallized from 12 parts of boiling alcohol in beautiful, practically colorless, transparent prisms melting at 179°–180°.

	Calculated for $C_9H_8ON_2S$.	Found.
N	14.58	14.47

2-Thio-3-phenylbenzalhydantoin,  .—The condensation of 2-thio-3-phenylhydantoin with benzaldehyde was carried out as follows: The hydanto n was dissolved in 6 parts of boiling glacial acetic acid containing 2 parts of fused sodium acetate, a slight excess of benzaldehyde was added and the mixture boiled for one and a half hours. On adding water and crystallizing the precipitated material from alcohol, yellow plates were obtained melting to a brownish yellow oil at 207°–208°.

	Calculated for $C_{18}H_{12}ON_2S$.	Found.
N	10.00	10.01

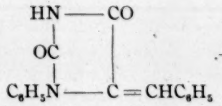
2-Ethylmercapto-3-phenylbenzalhydantoin,



.—Five grams of the above condensation product were converted into the ethylmercapto derivative in the same manner as in the case of the isomeric 1-phenyl compound. The product was practically insoluble in water and somewhat difficultly soluble in alcohol, from which solvent it formed yellow prisms melting to a clear oil at 165°–166°.

	Calculated for $C_{18}H_{16}ON_2S$.	Found. I.	Found. II.
N	9.09	9.01	9.15

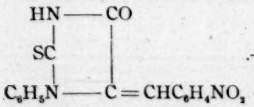
3-Phenylbenzalhydantoin,



.—When the above mercapto derivative was boiled with a mixture of alcohol and concentrated hydrochloric acid, mercaptan was evolved. After digesting on the steam bath for a number of hours, then evaporating to dryness, washing the residue with ether and crystallizing from alcohol, pale yellow plates were obtained which melted to a clear oil at 223°–224°.

	Calculated for $C_{16}H_{12}O_2N_2$.	Found. I.	Found. II.
N	10.61	10.55	10.48

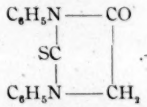
*2-Thio-3-phenyl-*p*-nitrobenzalhydantoin,*



.—The condensation of 2-thio-3-phenylhydantoin with *p*-nitrobenzaldehyde was carried out in

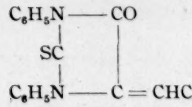
the same manner as with benzaldehyde. The yield of crude product was 92 per cent. of the calculated. It crystallized from 21 parts of hot glacial acetic acid and 35 parts of hot alcohol in orange-red prisms, which melted to a clear oil at 236°–237°.

	Calculated for $C_{16}H_{11}O_2N_2S$.	Found. I.	Found. II.
N	12.92	12.89	12.81

2-Thio-1,3-diphenylhydantoin,  .—This was prepared by heating phenylglycine or its ethyl ester with phenyl mustard oil in an oil bath at 150° until water or alcohol ceased being evolved. The yields were nearly quantitative. The diphenylthiohydantoin was crystallized from 50 parts of boiling alcohol, whereupon flat yellow prisms melting to a clear oil at 212° were obtained.

	Calculated for $C_{15}H_{12}ON_2S$.	Found.
N	10.45	10.46

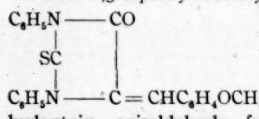
This hydantoin was found to be soluble in warm dilute sodium hydroxide, yielding an orange-yellow solution, from which it separated unaltered on adding an excess of hydrochloric acid.

2-Thio-1,3-diphenylbenzalhydantoin,  .—The condensation of thiodiphenylhydantoin with benzaldehyde was carried out as in the above cases. The product was purified by crystallizing from six parts of glacial acetic acid and then recrystallizing from 100 parts of alcohol. The alcoholic solution gave yellow needles melting to a clear, brown oil at 193°–194°. It was dried at 110° for analysis.

	Calculated for $C_{23}H_{18}ON_2S$.	Found. I.	II.	III.
C	74.16	73.48	....	....
H	4.49	4.14	....	....
N	7.87	....	7.78	7.86

This hydantoin was insoluble in cold alkali.

2-Thio-1,3-diphenylanisalhydantoin,



.—The mixture of thiodiphenylhydantoin, anisaldehyde, fused sodium acetate and glacial acetic acid, was heated somewhat longer than in the previous cases, as the condensation in this case appears to take place less readily. The product was difficultly soluble in glacial acetic acid, alcohol or acetone. From alcohol it formed poorly crystallized or indefinite granular masses. When crystallized from acetone it formed yellow needles which melted to a clear oil at 221°–222°.

	Calculated for $C_{23}H_{18}O_2N_2S$.	Found. I.	II.
N	7.25	7.05	7.11

NEW HAVEN, CONN.,
January, 1911.

[Contributions from the Kent Chemical Laboratory of the University of Chicago.]

ON THE ACTION OF NORMAL BARIUM HYDROXIDE ON *d*-GLUCOSE AND *d*-GALACTOSE.

BY FRED W. UPSON.

Kiliani[1] has maintained for some thirty years past that the formation of saccharinic acids, $C_6H_{12}O_6$, from the ordinary hexose sugars can be brought about only by the action of calcium hydroxide and that sodium, potassium and barium hydroxides do not lead to their formation. He ascribes, therefore, to the calcium a "specific" action. The work of Nef[2] on the action of alkaline hydroxides on the various hex-

[1] Ber. d. chem. Ges., **15**, 2960; **26**, 1650; **35**, 3530.
[2] Ann. Chem. (Liebig), **357**, 303; **376**, 1–111.

oses and pentoses, as well as my own work, shows conclusively that the results are not to be interpreted on the basis of any such "specific" action. All alkaline hydroxides give entirely analogous results when the concentration conditions are similar, but the ratio of the various saccharinic acids formed varies remarkably with the concentration of the alkali used.

The following pages contain an account of an investigation, carried out by me at the suggestion and under the direction of Professor Nef, on the action of normal barium hydroxide on *d*-galactose and *d*-glucose. I succeeded in isolating some of the saccharinic acids (many of which are new compounds) which Nef[1] obtained by the action of 8 N sodium hydroxide upon these same sugars. A striking difference, however, was observed in the relative amounts of the various products obtained. Whereas Nef isolated considerable amounts of the α- and β-metasaccharinic acids of the *d*-glucose and *d*-galactose series and also α- and β-isosaccharin, I obtained in each case, by the action of the more dilute alkali, only very small amounts of the first three named, optically active C_6-saccharinic acids, as well as relatively large amounts of *d,l*-lactic acid and of *d,l*-1,3-dihydroxybutyric acid. The amount of optically inactive saccharinic acids, formed from synthetic pentoses and hexoses,[2] was also relatively larger in my experiments, which, of course, explains the greater difficulty in isolating completely the optically active compounds formed. The experimental work was carried out largely on the basis of the work of Nef just published in Liebig's *Annalen der Chemie*.

EXPERIMENTAL PART.

1. d-*Galactose and Normal Barium Hydroxide.*

A hot solution of 100 grams of *d*-galactose, melting at 155°–160°, in 250 cc. of water was added slowly, in the course of half an hour, with constant shaking to a filtered solution of barium hydroxide containing 400 grams of crystallized barium hydroxide in 2200 cc. of water and maintained at a temperature of 60°. The solution turned yellow at first and finally

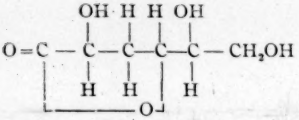
[1] Ann. Chem. (Liebig), **376**, 52–106.
[2] *Ibid.*, **376**, 9.

deep red-brown in color. After the addition of all of the sugar, the solution was at once placed in a large bath of boiling water and heated for eight hours, carbon dioxide, as well as air, being excluded by means of a condenser and receiver filled with water and connected with a soda-lime tube. No barium oxalate or carbonate was formed. The barium was removed by addition of the calculated amount of sulphuric acid and the precipitate filtered off and thoroughly washed. The combined filtrates were concentrated to about one liter by distillation under 20–30 mm. pressure and then treated so as to leave only a trace of barium in solution. On finally removing the water (under 25 mm., bath at 95°) a thick, dark brown gum remained. This was taken up in absolute alcohol and filtered from traces of barium salt. The weight of the nonvolatile saccharins, after complete removal of the alcohol, was 81 grams. These were resolved into two fractions by dissolving in 81 cc. of absolute alcohol and precipitating with twice this volume of ether. Only 4.6 grams of a gum, *D*, however, was deposited; the portion soluble in ether-alcohol amounted to 73.2 grams; it was dissolved in 100 cc. of water and extracted twenty times with about 150 cc. of ether each time. This effected a resolution into a portion remaining in the water, 37.5 grams, and into an ether-soluble portion, 31.6 grams. The 37.5 grams of gum remaining in the water was now further resolved, by solution in 37 cc. of alcohol and addition of 74 cc. of ether, into a fraction, *C*, 15.5 grams, insoluble in this mixture, and a soluble portion, 21.6 grams. The latter, dissolved in 20 cc. of water, gave, on twenty extractions with ether, 5.4 grams of ether-soluble gum, which was therefore united with the previous portion, 31.6 grams, mentioned above, giving a total of 37.0 grams crude C_3C_4-saccharinic acids (*A*), as a light, yellowish brown, mobile gum. The portion remaining in the water, 15.4 grams (*B*), as well as the above-mentioned fractions, (*C*), 15.5 grams, and (*D*), 4.6 grams, were all thick, very dark gums; it was therefore found necessary to remove the sugar tar present in these three fractions by acylation.[1] The acylation was

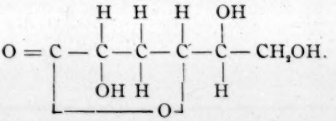
[1] Cf. Nef: Ann. Chem. (Liebig), **376**, 13–14.

carried out in the following manner: The gum was heated for nine hours at 100°–105° with three parts of acetic anhydride. The excess of acetic anhydride, as well as the acetic acid, were removed by distillation under 20 mm. pressure, the temperature of the bath being finally raised to 100°. The acylated gums were now separated from the insoluble tarry material by repeated extractions, first with cold and then with hot ether; they were then converted back into the free lactone gums, first by hydrolysis with five parts of water at 100°–110° for eight hours. After the removal of the water and acetic acid by distillation under 20 mm. pressure the gums were heated with 2 parts crystallized barium hydroxide and 2 parts water at 100° for eight hours. The barium was removed by precipitation with sulphuric acid and the water distilled off under 20 mm. pressure, a clear yellowish gum being left. All three fractions, (*B*), (*C*) and (*D*), mentioned above, were acylated in this manner; (*C*) and (*D*) were then united, giving 22.7 grams of acylated material soluble in ether and 5.7 grams of sugar tar. The former then gave, after complete hydrolysis, 13.2 grams light yellowish saccharins. Fraction (*B*) gave, on similar treatment, 21.7 grams acylated gums free from tar and then finally, on complete hydrolysis, 11.4 grams acid gums. The 13.2 grams of recovered saccharins mentioned above were resolved by digestion with 200 cc. of hot acetic ether into 11.6 grams of soluble gum and into 1.2 grams of insoluble material which was again acylated, yielding, finally, only 0.4 gram of saccharins free from tar. These, together with 1.5 grams of insoluble gum subsequently obtained from fraction (*A*) (see below), were now united with the 11.6 grams gum obtained from fraction (*B*). The total amount of saccharin free from tar thus obtained amounted, therefore, to 24.9 grams; these were now resolved, by digestion with a small amount of ether, into a soluble portion, I, 2.4 grams, and an insoluble portion, 19.6 grams. The latter was a thick, nonmobile, light yellow gum consisting mainly of C_5- and C_6-saccharinic acids, but still mixed with fairly large amounts of *d,l*-lactic acid and *d,l*-1,3-hydroxybutyrolactone. Accordingly, it was further resolved by digestion with acetic

ether, ether, etc., into three fractions: I, 6.7 grams soluble in 800 cc. cold ether, which, united with 2.4 grams of a similar product just mentioned above, made a total of 9.1 grams gum, I (see below); II, 4.5 grams soluble in 60 cc. cold ethyl acetate; and III, 8.6 grams insoluble in the same amount of the last-named solvent. II and III were then worked up for α- and β-*d*-galactometasaccharins,



and



The separation of the various saccharinic acids was accomplished mainly by means of brucine; accordingly, it was first necessary to determine, by titration, the amount of alkaloid needed for the various fractions; this was invariably done as follows: An aliquot portion containing from 0.2 to 0.3 gram of lactone gum was treated with an excess of 0.1 N sodium hydroxide and heated for ten minutes on the boiling water bath. The end point was then determined by titrating back with 0.1 N hydrochloric acid and phenolphthalein as an indicator. Gum III, 8.6 grams, was therefore made up with water to 500 cc.; 15 cc. of this solution, corresponding to 0.258 gram, required 17.35 cc. 0.1 N alkali for neutralization, whereas 0.258 gram $C_6H_{10}O_5$ requires only 15.93 cc.; small amounts of the lower saccharinic acids or their lactones must therefore still have been present. Finally it was always found best by experience to subsequently treat the main portion of a titrated gum with 5 per cent. less brucine than the amount demanded theoretically on the basis of the titration. Accordingly, the main portion of gum III was digested with

water and 20.5 grams of brucine for some hours on the boiling water bath, care being taken to heat one hour after complete solution of the alkaloid had taken place. The water was then removed by distillation at 50° under 10–20 mm. pressure; the 29.4 grams gummy brucine salts remaining gave, on crystallization from 50 cc. of 97 per cent. alcohol, 12.1 grams (in two crops) of crude *β-d*-galactometasaccharin brucine, melting from 105° to 120°. Fraction II, 4.5 grams, treated in a similar manner with 12.4 grams of brucine, etc., gave, besides 17.6 grams of gummy salts, only 1.65 grams of crystalline salts from alcohol, melting from 105°–120°. The combined unidentified gummy salts from II and III therefore amounted to 31.38 grams (see below). The total crude brucine salts of *β-d*-galactometasaccharin, 13.7 grams, melting at 105°–120°, recrystallized twice from three times their weight of 97 per cent. alcohol, yielded finally 6.0 grams of the pure salt melting at 137° to 138°.[1] This salt always crystallized rapidly from the above-named solvent in hard opaque nodules made up of masses of very fine needles. In order, however, to be absolutely sure of the purity of the final product the free lactone gum obtained from the purified brucine salt was first converted into the strychnine salt, etc. The salt was therefore digested in dilute aqueous solution with 1.5 times the required amount of aqueous barium hydroxide. The precipitated brucine was filtered off and well washed. The small amount of dissolved brucine was removed from the aqueous filtrate by fivefold extraction with benzene. The barium was then precipitated by means of sulphuric acid, the solution being finally left so that it still contained a trace of barium. The water was removed as usual by distillation *in vacuo* and the residual gum taken up in absolute alcohol and filtered from traces of barium salts, etc. This method was regularly used in recovering the acid gums from their brucine salts. The above-mentioned, practically pure brucine salt yielded in this way 1.6 grams of *β-d*-galactometasaccharin which, on long boiling with water and an excess of finely powdered strych-

[1] Cf. Nef: Ann. Chem. (Liebig), **357**, 304 and **376**, 75; also Killani: Ber. d. chem. Ges., **42**, 2609.

nine, gave 5.3 grams of crude strychnine salts. These, when crystallized from 12 cc. of 95 per cent. alcohol, gave 3.15 grams of voluminous, transparent, flat needles melting from 128° to 130° and possessing a specific rotation of $[\alpha]_D^{20}$ = —22°.95; i. e., 0.7386 gram salt and 17.5686 grams water, therefore p = 4.03 and d = 1.011, gave in a 1 dcm. tube $[\alpha]$ = —0°.935. These results agree very well with those recorded by Nef.[1] On setting free the gum from the strychnine salt in the usual way, 0.8966 gram of crude, almost colorless *β-d*-galactometasaccharin was obtained as a stiff gum which would not crystallize; it was identified by means of its specific rotation and then by conversion into its phenylhydrazide. Thus, 0.8966 gram lactone gum and 21.6435 grams water, therefore p = 3.98 and d = 1.011, gave in a 1 dcm. tube $[\alpha]$ = —2°.0, whence $[\alpha]_D^{20}$ = —49°.67.[2] The recovered gum was now converted into the phenylhydrazide by treatment at ordinary temperature with 0.9 cc. of phenylhydrazine and 0.9 cc. of absolute alcohol. The entire mass solidified spontaneously within a few hours through the formation of the hydrazide, but subsequently showed a tendency to become gummy when it was attempted to filter it. The hydrazide was found, therefore, in agreement with Nef's observations,[3] to be exceedingly unstable, but I finally succeeded in filtering off 0.85 gram of the substance in a crystalline condition; it was yellowish white in color, melted between 85° and 90° and gave the following results on analysis and optical investigation.

0.2047 gram dried *in vacuo* gave 0.3984 gram CO_2 and 0.1328 gram H_2O,

0.1987 gram substance gave 19.2 cc. dry N_2 at 21°.5 and 733.5 mm.

	Calculated for $C_{12}H_{18}O_8N_2$.	Found.
C	53.3	53.08
H	6.7	7.2
N	10.36	10.7

Optical rotation:

[1] Cf. Nef: Ann. Chem. (Liebig), **376**, 76.
[2] Cf. Nef: *Ibid.*, **376**, 71, 76.
[3] Cf. Nef: *Ibid.*, **357**, 304; **376**, 78.

0.7842 gram phenylhydrazide and 18.8194 grams water, therefore $p = 4.0$, $d = 1.011$, gave in 1 dcm. tube $[\alpha] = -0°.08$; whence $[\alpha]_D^{20} = -1°.85$.[1] The formation of *β-d*-galactometasaccharin from galactose and normal barium hydroxide is therefore established beyond a doubt.

The total gummy brucine salts left from fractions II and III amounted, as stated above, to 31.38 grams; these gave back, on treatment with barium hydroxide, etc., 9.5 grams of acid gums which were resolved by digestion with 50 cc. of hot acetic ether into 3.8 grams soluble (*b*) and 5.7 grams insoluble (*c*) saccharins. The (*b*) fraction, when boiled with water and an excess of quinine for eight hours, gave 12.1 grams of crude quinine salts. On digesting with 20 cc. of absolute alcohol only 0.8 gram of crude *α-d*-isosaccharin quinine (see below), melting at 170°–190°, remained undissolved and 3.2 grams of saccharin gums (*b*) were recovered from the alcohol-soluble quinine salts, which were united with a similar gum obtained from fraction (*A*) (see below). The fraction (*c*), 5.7 grams, gave back, after acylation, 4.0 grams of clear, light-colored gum; on dissolving this in 4 cc. of absolute alcohol and scratching with a glass rod, 0.76 gram of crude *α-d*-galactometasaccharin crystals separated out without seeding; these melted from 138° to 142° and were therefore united with a similar product, 0.4 gram, obtained from fraction (*A*) (see page 468); the mother liquors still contained, therefore, 3 grams of noncrystallizable saccharins (*C*).

On crystallizing the 1.16 grams of crude *α-d*-galactometasaccharin from 8 cc. of absolute alcohol, 0.6 gram of the pure substance separated out in fine white, glistening plates, melting between 143° and 144°. Nef[2] records 144° as the melting point of *α-d*-galactometasaccharin, and Kiliani[3] 142°. The analysis and optical investigation of my product gave the following results:

0.1989 gram substance, dried *in vacuo*, gave 0.3227 gram CO_2 and 0.1135 gram H_2O.

[1] Cf. Nef: Ann. Chem. (Liebig), **376**, 78.
[2] *Ibid.*, **357**, 304.
[3] Ber. d. chem. Ges., **16**, 2628.

	Calculated for $C_6H_{10}O_5$.	Found.
C	44.42	44.25
H	6.21	6.38

Optical rotation: 0.4272 gram α-metasaccharin and 9.3508 grams water, therefore $p = 4.36$ and $d = 1.011$, gave in a 1 dcm. tube $[\alpha] = -1°.89$, whence $[\alpha]_D^{20} = -42°.6$. The specific rotation of the substance is given as −48°.4 by Kiliani and as −45°.3 by Nef.[1] The identity of my product with α-*d*-galactometasaccharin was further confirmed by its conversion into the very characteristic phenylhydrazide. One and a quarter grams obtained from a previous experiment were dissolved in 1 cc. of water and 1 cc. of phenylhydrazine and 2 cc. of absolute alcohol were then added. After standing three days 1.65 grams of crude crystallized hydrazide separated out on the addition of ether. This compound, crystallized from 200 cc. of acetic ether, gave 1.3 grams of the pure product in white needles melting from 110°–112° and agreeing in all its properties with that described by Nef.[2] The analysis and optical investigation gave the following results:

Optical rotation: 0.5116 gram α-*d*-galactometasaccharin phenylhydrazide and 12.2000 grams water, therefore $p = 4.024$ and $d = 1.011$, gave in a 1 dcm. tube $[\alpha] = +1°.49$, whence $[\alpha]_D^{20} = +36°.6$. The specific rotation found by Nef[3] was +34°.38.

0.2100 gram substance dried *in vacuo* gave 0.4064 gram CO_2 and 0.1359 gram H_2O.

0.1802 gram substance gave 16.32 cc. dry nitrogen at 21° and 735.4 mm.

	Calculated for $C_{12}H_{18}O_5N_2$.	Found.
C	53.3	52.78
H	6.7	7.24
N	10.36	10.37

[1] Ann. Chem. (Liebig), **376,** 72.
[2] *Ibid.*, **357,** 304. Cf. also Kiliani: Ber. d. chem. Ges., **42,** 2608.
[3] Ann. Chem. (Liebig), **376,** 73.

The C_3,C_4-Saccharinic Acids; d,l-*Lactic Acid*, $CH_3—\overset{*}{C}HOH—COOH$, *and* d,l-*1,3-Dihydroxybutyric Acid*, $CH_2OH—\overset{*}{C}H_2—CHOH—COOH$.

Fraction I, 9.1 grams (page 462) gum fairly soluble in cold ether, was made up to 500 cc. with water; 10 cc., equivalent to 0.186 gram gum, required 19.1 cc. of 0.1 N alkali for neutralization. The remainder was treated with 5 per cent. less than the theoretical amount of brucine in the usual manner; 44.7 grams of crude brucine salts were obtained which, on crystallization from absolute alcohol, gave a total of 20.5 grams of crystalline salts (in three crops). These melted from 170°–195° and must therefore have consisted mainly of brucine 1,3-dihydroxybutyrate. Twenty-five and one-tenth grams of gummy noncrystalline brucine salts remained in the filtrates (see below).

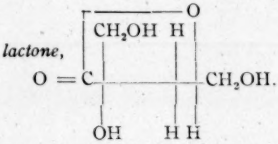
Fraction *A*, since it originally consisted of gums extracted from concentrated aqueous solutions by ether, obviously consisted mainly of *d,l*-lactic acid and 1-hydroxybutyrolactone. I found, in agreement with Nef, that it was impossible to separate these two substances by extraction from aqueous solution with ether—as is obvious from the following experiments: The gum (*A*), 37 grams, was dissolved in 144 cc. of water and extracted ten times with ether; 22.1 grams of gum were thus removed and these were then further resolved, by solution in four parts of water and tenfold extraction with ether, into 15.1 grams C_3,C_4-gums (I), soluble in ether, and 3.9 grams gum (*a*). The original aqueous solution, on tenfold further extraction with ether, gave 6.4 grams C_3,C_4-gums (II) and 9.8 grams gums still remained in the water solution; the latter, on digestion with 150 cc. ether, all dissolved except 1.5 grams referred to above (page 461). Therefore 8.3 grams of gum (*a'*) remained dissolved in this small amount of ether, which, with the 3.9 grams (*a*) just mentioned above, made a total of 12.2 grams mobile C_3,C_4-gums. The four fractions of C_3,C_4-gums (I), (II), (*a*) and (*a'*), were now treated separately with 5 per cent. less brucine than demanded on the basis of the titrations. On

crystallizing the salts several times from absolute alcohol, from two to three crops of high-melting crystalline salts were obtained in every case. Those which melted above 200° and crystallized in cubes were united and worked up as *d,l*-lactic brucine, 41.5 grams;[1] while those melting from 175° to 190° and crystallizing in prisms, 82.5 grams, consisted mainly of *d,l*-1,3-dihydroxybutyric brucine. In all, only 28.1 grams of noncrystallizable brucine salts were finally found in the alcoholic mother liquors of the four fractions named above; these were therefore united with 25.1 grams of similar salts left from fraction I (page 467). Fourteen and seven-tenths grams of thick, very dark brown saccharin gums were obtained from these by the usual treatment with barium hydroxide, etc. On shaking these with 500 cc. cold ether 6 grams of C_3,C_4-gums dissolved. The insoluble portion, 7.6 grams, gave back, after acylation, etc., 3.9 grams saccharins free from tar. These were now united with 3 grams of unidentified gums (*C*) mentioned on page 465 and obtained from the alcoholic mother liquors of *α-d*-galactometasaccharin; also with gums (*b*), 3.2 grams, from which *α-d*-isosaccharin had been removed by treatment with quinine; and finally with 4.0 grams of stiff, difficultly soluble gums subsequently obtained from the combined crude 1,3-dihydroxybutyric salts, obviously mainly *α*- and *β*-isosaccharin. The total amount of these unidentified gums was therefore 13.7 grams. On digestion with 200 cc. of acetic ether, 7.0 grams of these gums dissolved, which were subsequently further resolved by ether, etc., into 3 grams of soluble and 4.0 grams of insoluble gums; the insoluble portion, 6.7 grams, gave back, after acylation, 4.7 grams of saccharins free from tar, which, on dissolving in a small amount of alcohol, etc., gave 0.4 gram crude *α-d*-galactometasaccharin crystals already referred to on page 465. The mother liquors were now united with the 4.0 grams left undissolved on digestion of the acetic ether extract, 7.0 grams, with ether, as stated above, and finally 7.3 grams of saccharin gums were recovered; these were made up to 500 cc. with water; 15 cc., corresponding to 0.219

[1] Cf. Nef: Ann. Chem. (Liebig), **376**, 31.

gram gum, required 17.2 cc. 0.1 N alkali for neutralization. The main portion, treated with 21.06 grams of brucine, etc., gave 28.5 grams salts which on crystallization from alcohol gave 10.4 grams of crystalline brucine salts melting from 170° to 190°. These were therefore united with other salts of similar melting point. The gummy brucine salts, 17 grams, left in the alcoholic filtrate gave back 4.4 grams of saccharin gums which were boiled in water solution with an excess of quinine. On digesting the salts obtained, 16 grams, with absolute alcohol, 4.0 grams of crude *α-d*-isosaccharin quinine, melting at 195°–200°, remained undissolved. The alcohol-soluble quinine salts yielded 3.0 grams of nonmobile saccharin gum which was found to be optically inactive and was not further investigated.

α-d-*Isosaccharin*; *α-Hydroxymethyl-l-threo-1,4-dihydroxyvalero-lactone*,



The 4.0 grams of crude isosaccharinic quinine was united with 0.8 gram of similar salt obtained from fraction (*b*) (page 465) and then digested with 15 cc. of absolute alcohol. The melting point of the insoluble salt, 2.1 grams, was 195° to 200°. It gave with barium hydroxide, etc., 0.6 gram of crude α-isosaccharin, which only partially solidified. It was therefore further purified by conversion into the very difficultly soluble calcium salt, 0.3 gram being obtained. From this 0.1 gram of *α-d*-isosaccharin was finally obtained in snow-white crystals melting at 94°. It is also certain from Nef's experiments that the *α-d*-isosaccharin present in a complex mixture of C_3-, C_4-, C_5-, and C_6-saccharins never can be separated out completely by means of the quinine salt and Dr. Nef informs me that he was always able to detect *α-d*-isosaccharin in such mixtures by means of the difficultly soluble mixed brucine salt of *α-* and *β-d*-isosaccharin[1] even

[1] Ann. Chem. (Liebig), **376**, 57, 64.

when treatment with quinine had given no indication of its presence. This also explains why I was unable to find any *α-d*-isosaccharin in my experiments with *d*-glucose (see below). Finally, it should also be stated that I made no attempts to isolate the *β-d*-isosaccharin, also obviously present in my saccharin mixture, because this substance has not yet been isolated in a pure condition by Nef.[1]

The High-Melting Brucine Salts.

The total amount of crude 1,3-dihydroxybutyric brucine obtained from fractions I and II, (*a*) and (*a'*), was 82.5 grams, as stated above. These obviously still contained a fair amount of *d,l*-lactic acid, as well as *α*- and *β*-d-*isosaccharin*.[2] From this, 12.8 grams of crude 1-hydroxybutyrolactone was obtained by the usual treatment with barium hydroxide, but only 8.8 grams of this gum dissolved on shaking with 800 cc. of cold ether. The insoluble portion, 4.0 grams, which was dark and nonmobile and therefore consisted mainly of *α*- and *β-d*-isosaccharin, was now united, as already indicated on page 468, with other C_6-saccharin gums. The 8.8 grams of ether-soluble 1-hydroxybutyrolactone, including also 6.0 grams of ether-soluble C_3C_4-gums obtained from the gummy brucine salts (p. 468), were unfortunately united and then treated in the usual manner with 15 cc. each of phenylhydrazine and absolute alcohol. Contrary to expectations, no crystalline 1,3-dihydroxybutyric phenylhydrazide separated out. Nef has repeatedly observed that the presence of small amounts of other saccharins interferes greatly with the complete separation of 1,3-dihydroxybutyric phenylhydrazide. It is now obvious that the 1-hydroxybutyrolactone was contaminated with much lactic acid as well as C_6-isosaccharins. Accordingly, the gums, 14.0 grams, were recovered, after hydrolysis with barium hydroxide, etc.,[3] and again converted into the brucine salts. On crystallization from alcohol only 14.8 grams of crude 1,3-dihydroxybutyric brucine melting between 188° and 190° were obtained, and the salts left in

[1] Ann. Chem. (Liebig), **376**, 56.
[2] *Ibid.*, **376**, 31, 63.
[3] Cf. *Ibid.*, **376**, 33.

the alcohol gave back 9.3 grams gum, only 3.1 grams of which were soluble in cold ether. The remainder, which was thick and dark, then gave, after acylation, etc., 2.4 grams of thick, optically inactive gum, which was not further investigated. The 3.1 grams of ether-soluble gum was united with 3.0 grams of similar gums obtained by extracting some crude C_6-gums with ether, as mentioned on page 468. The total gums, 5.9 grams, as found by accurate determination, were made up to 500 cc. with water and titrated in the usual manner; 20 cc., corresponding to 0.228 gram, required 20.4 cc. of 0.1 N alkali for neutralization. On treating the main portion with 5 per cent. less than the calculated amount of brucine, 18.48 grams, and crystallizing the crude salts from alcohol, 5.3 grams more of crude 1,3-dihydroxybutyric brucine melting at 188° was obtained. The gummy brucine salts, from which no more crystalline salts could be obtained, gave back 3.3 grams of thick saccharin gum, which was not further investigated.

The total amount of crude 1,3-dihydroxybutyric brucine,[1] melting from 188° to 190°, was 30.5 grams in three crops of 14.8, 5.3 and 10.4 grams; these yielded 5.6 grams of crude 1-hydroxybutyrolactone, soluble in cold ether; it was dissolved in 5.6 cc. of absolute alcohol and 5.6 cc. of phenylhydrazine added. The mixture solidified after several days and gave 3.2 grams of snow-white powdery *d,l*-1,3-dihydroxybutyric hydrazide on washing with acetic ether. The substance melted[2] between 129° and 130° and gave the following results on analysis:

0.1921 gram substance, dried *in vacuo*, gave 0.4010 gram CO_2 and 0.1240 gram H_2O.

0.2072 gram substance gave 24.7 cc. dry nitrogen at 22°.5 and 736.7 mm.

[1] An optical investigation of a preparation of pure *d,l*-1,3-dihydroxybutyric brucine, obtained from the pure phenylhydrazide, and crystallizing in six-sided prisms, pointed at one end, and melting at 188° (cf. Nef: Ann. Chem. (Liebig), **376**, 31), gave the following results: 1.3458 grams salt and 31.7045 grams water, therefore $p = 4.05$, $d = 1.011$, gave in a 2 dcm. tube $[\alpha] = -2°.23$, whence $[\alpha]_D^{20} = -27°.23$.

[2] Cf. Nef: Ann. Chem. (Liebig), **376**, 33.

	Calculated for $C_{10}H_{14}O_5N_2$.	Found.
C	57.1	56.9
H	6.71	7.2
N	13.33	13.4

The total amount of crude *d,l*-lactic brucine[1] obtained, melting from 200° to 210°, was 41.5 grams, as mentioned above (page 468); this gave 8.6 grams of light-colored, mobile acid gum, which was heated in aqueous solution with excess of zinc carbonate for eight hours. The total amount of zinc lactate crystals obtained from the concentrated aqueous filtrate by addition of alcohol,[2] etc., was 7.1 grams, corresponding to 4.3 grams of free lactic acid. An analysis gave the following results:

2.0772 grams air-dried salt lost, on heating ten hours at 100° to 105°, 0.3768 gram H_2O.

0.2989 gram anhydrous salt gave, on ignition, 0.0993 gram ZnO.

	Calculated for $Zn(C_3H_5O_3)_2.3H_2O$.	Found.
H_2O	18.16	18.14
Zn	26.87	26.81

II. Dextrose and Normal Barium Hydroxide.

A hot solution of 100 grams *d*-glucose (melting at 145°–150°) was added slowly, in the course of half an hour, with constant shaking, to a filtered solution of 400 grams of crystallized barium hydroxide in 2000 cc. of water, maintained at a temperature of 60°. The mixture was then heated for five hours longer on a large bath of boiling water under the same conditions as described for *d*-galactose. No barium carbonate or barium oxalate was formed; the barium was removed as barium sulphate and the filtrates concentrated by distillation under 15 mm. pressure. The solution, containing finally only a trace of barium, was completely freed from water at the

[1] Racemic lactic brucine, made from Kahlbaum's lactic acid and brucine, crystallizes from 4 parts of absolute alcohol in colorless transparent cubes, melting at 210°. The specific rotation of the salt was found to be —29°.05 (cf. Ann. Chem. (Liebig), **376,** 31), i. e., 1.1847 grams salt and 28.6327 gram water, therefore $d = 1.011$; $p = 3.97$, in a 2 dcm. tube gave $[\alpha] = -2°.33$.

[2] Cf. Nef: Ann. Chem. (Liebig), **335,** 270.

temperature of the boiling water bath. The gum was taken up in absolute alcohol, filtered from traces of barium salts and the alcohol removed by distillation *in vacuo*. There remained 80.2 grams of a dark brown, somewhat mobile gum. The gum was dissolved in 80 cc. of absolute alcohol and on addition of 160 cc. of ether 10 grams of dark tarry material were precipitated. On removal of the alcohol and ether from the soluble portion 70 grams of gum remained. This was resolved by several extractions with ether into a fraction (*A*), 51.4 grams of which was completely soluble in 500 cc. of cold ether, and an insoluble portion, 18.7 grams. The two insoluble portions were united (fraction *B*), 28.7 grams, and then acylated in the manner already described. There remained 10.6 grams of sugar tar, and 34.2 grams of ether-soluble acylated gums were obtained, which yielded, on subsequent hydrolysis, 17.2 grams of fairly thick, light colored gums (*B*).

Fraction (A), 51.4 Grams, Mainly d,l-*Lactic Acid and* d,l-*1-Hydroxybutyrolactone.*

Nef[1] has shown that the sugars of the *d*-glucose series give much larger amounts of lactic acid on treatment with alkalies than do the sugars of the *d*-galactose series. It was therefore possible to remove at once a large portion of the lactic acid present in fraction (*A*) by conversion into zinc salts, etc. The total amount of crystallized zinc *d,l*-lactate ($Zn(C_3H_5O_3)_2 \cdot 3H_2O$), obtained in this way, was 41.6 grams, corresponding to 25.08 grams free lactic acid. The analysis of a portion of the zinc salt recrystallized from water gave the following results:

3.4277 grams air-dried salt lost, on heating for eight hours at 100°–105°, 0.6117 gram H_2O.

0.3985 gram anhydrous salt gave on ignition 0.1327 gram of ZnO.

	Calculated for $(C_3H_5O_3)_2Zn.3H_2O$.	Found.
H_2O	18.18	18.07
Zn	26.87	26.75

The aqueous alcoholic mother liquors from which, finally, no

[1] Ann. Chem. (Liebig), **357**, 300, and **376**, 53.

more crystallized zinc lactate could be obtained, gave back with hydrogen sulphide, etc., 19.3 grams of gum. This was resolved by means of cold ether into a soluble portion, 13.6 grams, and an insoluble fraction, 5.9 grams. The ether-soluble portion, 13.6 grams, was made up to 1000 cc. with water, and 15 cc., equivalent to 0.203 gram, required 19.6 cc. 0.1 N alkali for neutralization. On treating the remainder as usual, with 48.6 grams brucine, etc., two crops, 27.0 grams, of crude 1,3-dihydroxybutyric brucine, melting from 188° to 190°, were obtained. To these were added 12.1 grams more of similar melting salts (2.2 + 9.9 grams) subsequently obtained from the second fraction (*B*) (see below). These then gave 8.3 grams of crude 1-hydroxybutyrolactone, which, on the usual treatment with 8 cc. each of phenylhydrazine and absolute alcohol, gave 5.3 grams of pure *d,l*-1,3-dihydroxybutyric phenylhydrazide, melting at 129°–130°.

0.1921 gram substance, dried *in vacuo*, gave 0.4010 gram CO_2 and 0.1240 gram H_2O.

0.2072 gram substance gave 24.7 cc. dry N_2 at 22°.5 and 736.7 mm.

	Calculated for $C_{10}H_{14}O_3N_2$.	Found.
C	57.1	56.9
H	6.71	7.2
N	13.33	13.4

The alcoholic mother liquors from the first two crops of 1,3-dihydroxybutyric brucine named above still contained about 35 grams of brucine salts; these gave in all 20 grams of low-melting (100°–120°) crystalline salts which are referred to later on. The noncrystallizable salts still left in the alcoholic filtrates gave back 3.2 grams of thick nonmobile saccharin gums, which were then treated as described below.

The above-mentioned saccharin gums, 5.9 grams, remaining undissolved in ether, were now resolved by means of 50 cc. of hot acetic ether into an insoluble portion, 1.4 grams, and a soluble fraction, 3.9 grams. The latter gave no crystalline salts on treatment with brucine or quinine and finally 3.3 grams of acid gums (*b*) were recovered. This fraction,

as well as 1.4 grams insoluble gum, was then united with various other C_6-saccharin gums as described below.

When fraction (*B*), 17.2 grams, was boiled with water and an excess of finely powdered strychnine for ten hours, 60.2 grams of crude strychnine salts were obtained, but no crystalline salts were obtained by dissolving these in 60 cc. of alcohol. The saccharin gums were therefore again recovered, 16.8 grams, and resolved by digestion with much hot ether into 10.6 grams soluble gums and 6.2 grams insoluble saccharins. The latter was now united with 1.4 grams of a similar gum obtained, as already mentioned (p. 474), from fraction (*A*). Only 3.2 grams of saccharins free from tar were recovered from these after acylation, etc., which were now united with the 10.6 grams of ether-soluble gums mentioned above, 13.8 grams gum in all being thus obtained. On shaking these with 200 cc. of cold ether, 1.6 grams dissolved and gave with brucine, etc., 2.2 grams of 1,3-dihydroxybutyric brucine melting from 188° to 190°, which was therefore united with other salts of similar melting point, as already stated. The insoluble fraction, 12.2 grams, titrated too high for C_6-saccharins. It was made up to 500 cc. with water and 10 cc., equivalent to 0.22 gram gum, required 19.0 cc. of 0.1 N alkali for neutralization; obviously much 1-hydroxybutyrolactone was still present. On converting the remainder with 35 grams of brucine into salts and crystallizing these from alcohol, 9.9 grams more 1,3-dihydroxybutyric brucine, melting at 187°–190°, were obtained and therefore united with the corresponding salt, 27.1 grams, obtained from fraction (*A*), as already described above. There were also subsequently obtained 2.6 grams of a low-melting (100° to 120°) crystalline salt which was therefore united with 20 grams of similar salt obtained from fraction (*A*); these then gave, with barium hydroxide, etc., 4.2 grams of lactone gums. On boiling these with water and an excess of powdered strychnine and dissolving the 14.4 grams of crude salts thus obtained in 30 cc. alcohol, only 0.8 gram of crude β-dextrometasaccharinic brucine was obtained; the rest of the material then gave back 3.3 grams of lactone gum (*c*).

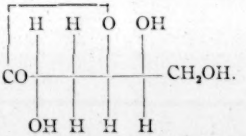
The gummy brucine salts still left in the alcoholic filtrates of fraction (*B*) similarly gave back 5.4 grams of lactone gum which were united with 3.2 grams of gum obtained from the noncrystalline brucine salts of fraction (*A*) and then boiled with water and an excess of powdered strychnine; on dissolving the 26.0 grams of crude salts thus obtained in 52 cc. of 95 per cent. alcohol, 3.7 grams of crude β-dextrometasaccharinic strychnine, decomposing between 178° and 185°, were obtained. These, together with the 0.8 gram similar salt mentioned above, gave back only 0.4 gram of β-dextrometasaccharin because of the presence of much free strychnine. The gummy strychnine salts left in the alcoholic filtrates similarly gave back 7.8 grams of free lactone gums; titration of a small portion of these at this point indicated the presence of C_3C_4-saccharins, which it seemed probable would interfere with the crystallization of the strychnine salts. This gum was therefore extracted several times with hot ether, 4.4 grams finally remaining undissolved. The ether extract was discarded. The 4.4 grams gum dissolved in water was then heated for four hours in an open dish on a boiling water bath in order to volatilize the 1-hydroxybutyrolactone and lactic acid still present. By this process the amount of the gum was reduced to 3.2 grams; it was now first treated with 7.8 grams of brucine and on crystallizing the 11 grams of crude salts obtained from 22 cc. of alcohol, 3.0 grams of crude β-dextrometasaccharin brucine, melting from 140° to 150° and possessing a specific rotation of —30°, were obtained. This shows that about 30 per cent. of the α-dextrometasaccharin salt was present.[1] The gum recovered from the salts still left in the alcoholic filtrates was not further investigated.

The 3.3 grams of gum (*c*) (p. 475) obtained from the noncrystalline strychnine salts was now united with fraction (*b*) (p. 474), 3.3 grams, and these were then diluted with water to 500 cc.; since 15 cc., corresponding to 0.198 gram gum, required 16.7 cc. 0.1 N alkali for neutralization, whereas 0.198 gram C_6-saccharin requires only 12.2 cc., some C_3,C_4-saccharinic acids must still have been present. The gum

[1] Cf. Nef: Ann. Chem. (Liebig), **376**, 92.

was therefore dissolved in 12 cc. of water and extracted twenty times with ether. The 4.4 grams gum which remained in the aqueous solution was then heated with water in an open dish for four hours on the boiling water bath and thus finally 3.3 grams of gums free from C_3,C_4-saccharins were obtained. These were converted by means of 7.8 grams of brucine into salts and yielded on the first crystallization from 96 per cent. alcohol 1.6 grams of practically pure β-dextrometasaccharinic brucine melting between 145° and 150° and possessing a specific rotation of —33°. The 3.0 grams of saccharin gums recovered from the alcoholic mother liquors were found to have no effect on polarized light and were therefore not further investigated.

β-Dextrometasaccharin,



The total amount of crude β-dextrometasaccharinic brucine obtained in two lots (see above), was 4.6 grams; these yielded 0.8 gram of crude β-dextrometasaccharin gum which was then united with 0.4 gram of a similar gum obtained from the crude β-dextrometasaccharinic strychnine salts (p. 476). These were now boiled with water and an excess of powdered strychnine and finally gave, on crystallization of the salts obtained from alcohol, 2.1 grams of crude β-dextrometasaccharinic strychnine, melting with decomposition between 185° and 190°. This yielded 0.5 gram of crude β-dextrometasaccharin as a gum which would not crystallize. It was therefore converted into the calcium salt in the usual way and gave, on crystallization from concentrated aqueous solution by the addition of alcohol, 0.35 gram of white, heavy, crystalline needles of pure calcium β-dextrometasaccharinate. An optical investigation of the salt, dried *in vacuo* over sulphuric acid, gave the following result: 0.3545 gram calcium salt and 17.1648 grams water, therefore p = 2.03 and d = 1.010, gave in a 1 dcm. tube $[\alpha]$ = —0°.48,

whence $[\alpha]_D^{20} = -23°.41$. Nef[1] records $-23°.25$ as the specific rotation of this salt. The salt was now treated in aqueous solution with the theoretical amount of oxalic acid and the crude β-dextrometasaccharin then taken up in absolute alcohol and filtered from traces of calcium salt. A pure, almost colorless gum finally remained, which quickly solidified to a mass of fine, white, feathery crystals on seeding with a trace of the pure lactone; 0.12 gram of the substance, melting from 90° to 92°,[2] was obtained on washing well with acetic ether. An optical investigation gave the following results: 0.1264 gram β-dextrometasaccharin and 3.2068 grams water, therefore $p = 3.79$ and $d = 1.011$, gave in a 0.5 dcm. tube $[\alpha] = +0°.24$, whence $[\alpha]_D^{20} = +12°.53$. The result is somewhat higher than that recorded by Nef,[2] $+8°.2$, but is probably due to the small amount of material used in my determination. The gum recovered from the aqueous solution after making the optical observations was now treated with 0.1 cc. of phenylhydrazine and 0.2 cc. of absolute alcohol. The mixture solidified on standing overnight; 0.096 gram of the hydrazide was obtained in almost white, flaky crystals on filtering and washing with acetic ether; these melted from 125° to 130° and gave $[\alpha]_D^{20} = -29°.44$; i. e., 0.0962 gram hydrazide and 2.3673 grams water, therefore $p = 3.9$, $d = 1.011$, gave in a 0.25 dcm. tube $[\alpha] = -0°.29$, whence $[\alpha]_D^{20} = -29°.44$.[2] These results therefore establish beyond a doubt the formation of β-dextrometasaccharin from *d*-glucose and normal barium hydroxide.

I did not succeed in isolating any α-dextrometasaccharin or α- and β-*d*-isosaccharin in my experiments with *d*-glucose but these must obviously also have been present. It is clear that the presence of relatively larger amounts of optically inactive C_5- and C_6-saccharinic acids, formed from synthe ic, optically inactive pentoses and hexoses, has made the detection and complete isolation of the optically active C_6-saccharinic acids present a problem of very unusual experimental difficulty.

[1] Nef: Ann. Chem. (Liebig), **376**, 95.
[2] *Ibid.*, **376**, 96.

In conclusion the author would express sincere gratitude to Dr. Nef for his continued help and encouragement throughout the course of this work.

STUDIES IN ESTERIFICATION.

IV. THE INTERDEPENDENCE OF LIMITS AS EXEMPLIFIED IN THE TRANSFORMATION OF ESTERS.[1]

By E. Emmet Reid.

The classical experiments of Berthelot and Péan de St. Giles,[2] and the more exact work of Menschutkin[3] and Lichtz[4] have shown that when an organic acid is heated with an alcohol esterification takes place and a well-defined limit is reached, and that the same limit may be reached by heating the corresponding ester with water:

$$(1) \qquad CH_3COOH + HOC_2H_5 \rightleftarrows CH_3COOC_2H_5 + H_2O.$$

In the case of acetic acid and ethyl alcohol, according to Menschutkin, if the acid and alcohol are present in equivalent amounts, equilibrium is reached when 66.57 per cent. of these have been transformed into ester and water. The same thing may be looked at in another way. It may be regarded as a case of partition and 66.57 and 33.43 be considered as partition factors. Then the acetyl, $CH_3CO.$, is partitioned between the .OH and .OC_2H_5 groups. It is to be understood that it is not meant that such detached groups are present in the mixture. In this discussion no new theory of esterification is proposed and no one of the theories which have been put forth is favored or disfavored. The acid and alcohol may be written $CH_3COO.H$ and $HO.C_2H_5$ and the same equations set up in terms of these groups. Thus if .OH and .OC_2H_5 groups are present in equal number, as in a mixture of equivalent amounts of acetic acid and alcohol, the relative amounts

[1] This Journal, **41**, 483; **43**, 489; **45**, 38.
[2] Ann. chim. phys., [3] **65**, 385–422; **66**, 5–218; **68**, 225–359.
[3] Ber. d. chem. Ges., **10**, 1728; **11**, 1507.
[4] This Journal, **17**, 27; **18**, 590.

of acetyl combined with these two groups will be given in this form:

$$(2) \qquad \frac{CH_3CO.OC_2H_5}{CH_3CO.OH} = \frac{66.57}{33.43} = \frac{1.991}{1}$$

This number, 1.991, is the square root of k, the equilibrium constant given by the usual equation,

$$\frac{x^2}{(A-x)(B-x)} = k,$$

in which A and B are the original concentrations of acid and alcohol and x is the amount of ester at the limit. In case the acid and alcohol are not present in equivalent amounts, the actual amounts of $.OH$ and $.OC_2H_5$ present in the mixture, whether derived from $CH_3CO.OH$ or $H.OH$, or from $H.OC_2H_5$ or $CH_3CO.OC_2H_5$, are used in the calculation. Using the customary brackets to denote concentrations, we have at the limit:

$$(3) \qquad \frac{[CH_3CO.OC_2H_5]}{[CH_3CO.OH]} = \frac{[.OC_2H_5] \times 66.57}{[.OH] \times 33.43} = \frac{[.OC_2H_5] \times 1.991}{[.OH] \times 1}$$

In ordinary partition, such as that of a solute between two immiscible solvents, say iodine in ether and water, the solubility of the solute in the two solvents is more or less influenced by the fact that each solvent is somewhat altered by having dissolved some of the other solvent. The equilibria, particularly when several solutes and several solvents are present, are very complex, but in this, which we may call chemical partition, no such troubles arise. In the case of ester formation even such substances as hydrochloric acid, which enormously accelerate the approach to equilibrium, do not alter the location of the equilibrium point, or, in terms of the above, do not change the partition ratio 1.991 : 1. Acree[1] believes that catalysts which will change the equilibrium point may yet be found, but none have so far been reported, except, of course, those which form some sort of a combination with one or more of the reaction products. It is then not likely that the presence of some methyl alcohol

[1] This Journal, **38**, 353.

would alter the above equilibrium between acetic acid and ethyl alcohol, that is, the partition of acetyl between hydroxyl and ethoxyl should not be affected by the presence of methoxyl, even though the methyl alcohol acts on its own account to produce some methyl acetate.

In the case of methyl alcohol, according to Menschutkin, if an equivalent amount of acetic acid is present, esterification reaches the limit at 69.52 per cent. of ester. Writing this in the form used above we have:

$$(4)\quad \frac{[CH_3CO.OCH_3]}{[CH_3CO.OH]} = \frac{[.OCH_3] \times 69.52}{[.OH] \times 30.43} = \frac{[.OCH_3] \times 2.281}{[.OH] \times 1}$$

If a quantity of acetic acid is heated with a mixture of methyl and ethyl alcohols, and if the presence of neither of the alcohols influences the equilibrium between the other alcohol and its ester, we will have at the limit:

$$[CH_3CO.OCH_3] : [CH_3CO.OC_2H_5] : [CH_3CO.OH] :: [.OCH_3] \times 2.281 : [.OC_2H_5] \times 1.991 : [.OH] \times 1.$$

Hence the amounts of methyl and ethyl esters present will be in the proportion

$$[CH_3CO.OCH_3] : [CH_3CO.OC_2H_5] :: [.OCH_3] \times 2.281 : [.OC_2H_5] \times 1.991.$$

Now, if under these same conditions, ethyl acetate is transformed directly into methyl acetate by methyl alcohol, and *vice versa*, according to the formulation:

$$(5)\quad CH_3CO.OC_2H_5 + HOCH_3 \rightleftharpoons CH_3CO.OCH_3 + HOC_2H_5,$$

then the equilibrium, or partition, in this case will be represented by the equation

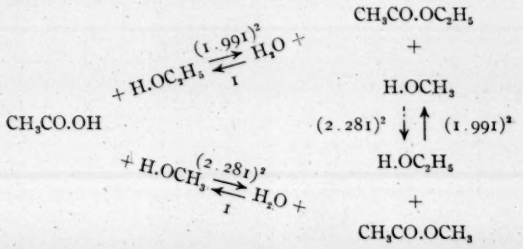
$$(5)\quad \frac{[CH_3CO.OCH_3]}{[CH_3CO.OC_2H_5]} = \frac{[.OCH_3] \times 2.281}{[.OC_2H_5] \times 1.991}.$$

This must be the case, else no equilibrium could be reached in the mixture, and there would be perpetual motion, a con-

tinuous transformation of acetic acid into one of the esters, this ester into the other ester and this back into the acid.

If we suppose that the esters in the above mixture are in equilibrium in the above ratio in presence of acetic acid it is difficult to see that this equilibrium between the two esters would be altered by the withdrawal of the acid. Hence we would expect that in case reaction (5) takes place between the esters and alcohols alone, that is, in the absence of acetic acid or of water, the same equilibrium point should be reached. That is, the partition of the acetyl between the methoxyl and ethoxyl is independent of other substances.

The three reactions involved may be represented in a triple formulation. The relative velocities of the reactions between equivalent quantities of the reacting substances are represented by numerals adjacent to the arrows, according to a notation introduced in a previous article.[1]



According to the above reasoning, when ethyl alcohol is heated with a methyl ester, and *vice versa*, the equilibrium point can be calculated from measurements made with the corresponding acid and the two alcohols, one at a time. Of course, the same reasoning may be expected to hold with other alcohols and their esters, as well as with mercaptans and their esters, and, possibly, also with amides, anilides, etc., in so far as other influences do not interfere.

Looking at esterification from the other side, it appears that the OC_2H_5 group is partitioned between the H. and

[1] This Journal, **43**, 502.

CH_3CO groups. According to this, if one acid acts on the ester of another acid, there should be equilibrium at a point which can be calculated from the esterification limits found by taking the two acids one at a time with the alcohol involved.

As, in inorganic chemistry, we have the partition of an acid between two bases and of a base between two acids, so in organic chemistry we must have the partition of an acid between two alcohols and of an alcohol between two acids. In both cases we may calculate the partition from other data, but as the experimental work below shows, this calculation is much simpler in the case of organic acids and alcohols. We may expect to find a volatile alcohol, or acid, being driven out by a nonvolatile alcohol or a nonvolatile acid. Finally, we may expect to find double decomposition between two esters such as ethyl acetate and methyl propionate, in which the acids and alcohols are different.

The limits found by Menschutkin[1] with acetic acid for the various alcohols are set down in Table I, and under these are put the partition factors calculated as above:

Table I.

	Methyl.	Ethyl.	Propyl.	*n*-Butyl.	Isobutyl.
Limit	69.52	66.57	66.85	67.30	67.38
Factor	2.231	1.991	2.016	2.058	0.266
	Octyl.	Cetyl.	Allyl.	Benzyl.	Styronyl.
Limit	72.34	80.39	59.41	60.75	64.58
Factor	2.615	4.099	1.464	1.548	1.820

In case a mixture of any number of these alcohols were heated with acetic acid, the amounts of the several esters formed and of the acid remaining free, when equilibrium is finally reached, may be calculated by multiplying the amount, expressed in equivalents, of each alcohol present by the proper factor from this table, summing up all these products, adding the amount of acid, also expressed in equivalents, multiplied by 1, and dividing the individual products by this sum. Thus, suppose 2 equivalents of methyl, 3 of ethyl, 3 of propyl and

[1] Ber. d. chem. Ges., **10**, 1728; **11**, 1507.

2 of isobutyl alcohols to be heated with 5 equivalents of acetic acid, at equilibrium we should have a mixture of esters and free acid, the components of which are thus found to be $2 \times 2.281 + 3 \times 1.991 + 3 \times 2.016 + 2 \times 2.066 + 5 \times 1 = 25.715$. Then the amounts of the several esters, expressed in equivalents, will be

$$\frac{2 \times 2.281}{25.715}, \frac{3 \times 1.991}{25.715}, \frac{3 \times 1.016}{25.715} \text{ and } \frac{2 \times 2.066}{25.715},$$

and the amount of acid remaining will be

$$\frac{5 \times 1}{25.715}.$$

In Table II are given similar data for acids with ethyl alcohol, the limits being taken from the work of Berthelot and Péan de St. Giles,[1] Menschutkin[2] and Lichtz.[3]

Table II.

	Acetic.	Chloracetic.	Dichloracetic.	Trichloracetic.	Butyric.	Tartaric.	Succinic
Limit	66.57	68.65	71.22	74.00	70.2	66.6	66.0
Factor	1.991	2.190	2.475	2.846	2.356	1.995	1.941

	Valeric.	Stearic.	Pyrotartaric.	Suberic.	Sebacic.	Citric.	Benzoic.
Limit	65.8	72.0	67.2	65.7	66.3	66.6	66.6
Factor	1.924	2.577	2.049	1.916	1.967	1.995	1.991

Equilibrium constants, from which limits may be calculated, for some aliphatic acids and a number of substituted benzoic acids are given in articles by Rosanoff and Prager[4] and by Prager.[5] Benzoic acid was studied by Berthelot and Péan de St. Giles,[6] who showed that it gave sensibly the same limit as acetic acid, 66.3 to 66.8 per cent., and hence the same equilibrium constant, approximately 4, instead of which Rosanoff and Prager find 0.4 (!), corresponding to a limit of about 38 per cent. esterification. They evidently did not

[1] Ann. chim. phys., [3] **65**, 234; **66**, 5–128; **68**, 225.
[2] Ber. d. chem. Ges., **10**, 1728; **11**, 1507.
[3] THIS JOURNAL, **17**, 27; **18**, 590.
[4] J. Am. Chem. Soc., **30**, 1895.
[5] *Ibid.*, **30**, 1908.
[6] Ann. chim. phys., [3] **66**, 36, 52, 73, 101; **68**, 229, 267.

reach the limit on account of insufficient heating or else saponified some of the ester during titration. Since most of the acids with which they worked approached equilibrium much more slowly than benzoic acid, doubt is thrown on their other equilibrium constants, and as they used these in computing the reaction velocities, the latter are also open to question.

Unfortunately, we have data for the alcohols with only one acid and for the acids with only one alcohol, and hence have no means of knowing how an acid other than acetic would be partitioned between methyl and ethyl alcohols, but if such another acid, such as benzoic acid, is partitioned between hydroxyl and ethoxyl in the same ratio, i. e., has the same esterification limit as acetic acid, it is safe to assume that it will be partitioned between methoxyl and ethoxyl in the same ratio as is acetic; otherwise, this assumption is not safe. A comprehensive study of limits with a large number and variety of acids, each with a large variety of alcohols, is very desirable.

The question here considered, the interdependence of limits, is regarded as a general one, being nothing more than an application of the mass law and holding for reactions in inorganic as well as for those in organic chemistry, but it is here discussed in terms of the esters since they furnish a concrete example which is capable of experimental approach.

The question of the partition of an acid between two alcohols has been studied by the aid of the reciprocal transformations of the ethyl and methyl esters of benzoic acid, since these esters, being practically insoluble in water, are easily washed free from acid, and other impurities soluble in water, with little loss of the esters. The fact that their boiling points are far removed from those of water and of the corresponding alcohols also facilitates their purification. That they have so nearly the same boiling points, 199° and 212°, is also an advantage, since there is little danger of a change of composition of a mixture of the two esters on account of the evaporation of the more volatile constituent. The two esters differ sufficiently in density, 1.08714–1.04475, or 0.04239, to furnish an analytical method for the determination of the composition of a mixture of the two.

Since esterification limits may be determined far more accurately in the case of an acid such as acetic acid, which is readily soluble in water, the partition factors calculated above from the work of Menschutkin on acetic acid are assumed to hold for benzoic acid. Even if the partition factors are somewhat different for benzoic acid, their ratio cannot differ much from the ratio of those for acetic acid.

The question of the partition of an alcohol between two acids has been studied by the aid of the ethyl esters of benzoic and *p*-brombenzoic acids. These esters have the above-mentioned advantages of insolubility and high boiling points and a far greater difference in densities, 1.4385–1.0447, or 0.3938, so that 1 unit in the fourth decimal place corresponds to only 0.02 per cent. in the composition of a mixture of the two esters. This renders the density method even more accurate and permits the use of smaller samples of esters. The slight solubility of *p*-brombenzoic acid, 0.0037 gram in 100 cc. of water at 25°, about 15 times the solubility of barium sulphate, makes the washing of this acid out of a mixture of esters somewhat tedious, but is an advantage since it renders the testing of the completeness of the washing easy and certain.

One experiment has been tried on the replacement of acetic acid in benzyl benzoate, using the density method for the analysis of the resulting mixture.

Also a little work has been done on the question of double decomposition of two esters. For this, ethyl benzoate and benzyl acetate have been used since the boiling points of ethyl acetate, 77°, and that of benzyl benzoate, 323°, are sufficiently far removed from those of the other two esters, both of which boil near 212°, to render their separation possible.

The question of the partition of an acid between an oxygen and a sulphur alcohol has been studied in the transformation of ethyl benzoate into ethyl thiolbenzoate by mercaptan and of the thiol ester into the oxygen ester by alcohol. In this case the two esters chosen have the above-mentioned advantages of insolubility in water and high boiling points. The difference in density of the two esters is sufficient for the ap-

plication of the density method of analysis, but on account of the difficulty of preparing considerable quantities of the thiol ester, the estimation of the sulphur content of the reaction product has been used instead.

In the partition of an acid between two alcohols some work has been done both with hydrochloric acid and with sodium alcoholates as catalysts, but since in the one case the equilibrium is disturbed by the unequally rapid action of the hydrochloric acid on the two alcohols to form alkyl chlorides, and in the other by the unequal distribution of the sodium between the two alcohols to form alcoholates, and by the formation of dense precipitates by the addition of even small percentages of sodium alcoholates to the esters, for accurate determinations of the partition factors, or equilibrium constants, recourse must be had to the experiments without catalysts Since, in the absence of any catalyst, even simple esterification proceeds very slowly at moderate temperatures, the transformation of esters, which may be regarded as the esterification of esters, may be expected to be a slow reaction unless accelerated by elevation of the temperature. Accordingly, for this part of the work, temperatures of from 200° to 230° have been used.

Partition of an Acid between Two Alcohols, or Ester Transformation.—A number of more or less isolated cases of the transformation of the ester of one alcohol into the ester of another alcohol are given in the literature, but it is difficult, if not impossible, to bring all of these together. In this line the classical work is that of Claisen in 1887.[1] He heated on the water bath benzyl benzoate with methyl alcohol and methyl benzoate with benzyl alcohol but got no reaction in either case. When he added sodium methylate to the former mixture and sodium benzylate to the latter, the mixtures solidified, and on acidifying with acetic acid transformation was found to have taken place. These transformations he assumed had taken place through the formation of the ortho compounds according to the scheme

[1] Ber. d. chem. Ges., **20, 646.**

(8) $C_6H_5C(=O)OC_7H_7 + NaOCH_3 \rightleftharpoons C_6H_5C(ONa)(OCH_3)OC_7H_7 \rightleftharpoons C_6H_5C(=O)OCH_3 + NaOC_7H_7.$

In the formation of benzyl benzoate from benzaldehyde, which he considered as taking place accord ng to the formulation

(9) $2C_6H_5CHO + C_6H_5CH_2ONa \longrightarrow C_6H_5C(OC_7H_7)(OC_7H_7)ONa \longrightarrow C_6H_5C(=O)OC_7H_7 + NaOC_7H_7,$

he noted that a small amount of sodium benzylate, since it is regenerated in the reaction, might transform an indefinite amount of the benzaldehyde.[1] His reasoning evidently applied equally well to the ester transformation, but he did not call attention to this.

Seelig,[2] in preparing benzyl acetate, heated benzyl chloride and potassium acetate in sealed tubes with ethyl alcohol. He noticed the formation of ethyl acetate and found that the higher he heated the mixture, the less benzyl acetate and the more benzyl alcohol he obtained. He supposed that the ethyl acetate was formed by the action of free acetic acid on the alcohol, but it is more likely that it was formed by the action of the ethyl alcohol at the temperature of 150°, at which he worked, on the benzyl acetate, giving ethyl acetate and benzyl alcohol.

Kossel and Kruger[3] showed that ethyl salicylate was formed from salol and sodium ethylate.

Henriques[4] studied the transformation of glycerides in alcoholic solution by sodium ethylate and showed that with as little as 15 per cent. of the alkali necessary for their saponifica-

[1] *Loc. cit.*, p. 650.
[2] J. prakt. Chem., [2] **39**, 157.
[3] Z. physiol. Chem., **18**, 321.
[4] Z. angew. Chem., **1898**, 338–345.

tion, the glycerides were completely transformed into the corresponding ethyl esters. He, as well as Kossel and Kruger, adopted the explanation of Claisen given above. The question of mechanism was further discussed by Goldschmidt.[1]

Shaklee[2] obtained benzyl acetacetate, almost quantitatively, by heating 20 grams benzyl alcohol and 40 grams ethyl acetacetate to 160°. Bacon[3] verified this, and prepared benzhydryl acetacetate by heating 50 grams benzhydrol with 100 grams ethyl acetacetate for 1 hour at 150°, the more volatile ethyl alcohol distilling over in both cases. These two experiments are of value in that they show that the reaction goes to completion in case one of the alcohols is volatile and cannot remain in the reacting mixture at the temperature used.

Much quantitative work on the transformation of esters, using sodium alcoholates as catalysts, has been done by Kremann[4] and Pfannl.[5] The former worked mainly with polyacetates, particularly triacetin, and finally came to the conclusion that a dynamic equilibrium exists in the sense of the formulation

$$(10)\quad C_3H_5(OOCCH_3)_3 + 3C_2H_5OH \underset{12.7}{\overset{1}{\rightleftharpoons}} C_3H_5(OH)_3 + 3CH_3COOC_2H_5.$$

His analytical method was to distil the ethyl acetate off into an excess of standard alkali, the excess of which was subsequently titrated back. The nonvolatile triacetin remaining in the distillation flask was likewise determined by saponification. He found the backward velocity in the above reaction to be 12.7 times the forward velocity, the individual determinations running from 7.7 to 17.3. On treating a quantity of ethyl acetate with a large excess of glycerol and some alcoholic soda 20 per cent. of the ester was transformed into triacetin. With certain complex acids he considered the possibility of

[1] Z. Elek. Chem., **10**, 221.
[2] Unpublished work quoted by Bacon and by Higley. THIS JOURNAL, **33**, 39; **37**, 310.
[3] THIS JOURNAL, **33**, 79.
[4] Monatsh., **26**, 783–822; **27**, 410–630; **29**, 23–44.
[5] *Ibid.*, **31**, 301 (1910).

steric hindrance to ester transformation. Sudborough[1] has shown that there is such hindrance in the case of doubly ortho-substituted acids.

Pfannl[2] showed that ester transformation is perfectly general, and that all of the reactions are reversible. He worked with the methyl, ethyl, and propyl esters of terephthalic, benzoic, and oxalic acids. He used "at least ten parts of the alcohol" to one part of the ester, which would mean 20 to 30 molecules of the alcohol to one of the ester. Since dimethyl terephthalate requires 100 parts of methyl alcohol for its solution, while the corresponding ethyl and propyl esters are very soluble in methyl alcohol, his method of work was to dissolve a quantity of the ethyl or propyl ester in 20 parts of methyl alcohol, adding the desired amount of sodium methylate, and note the time until crystals of the methyl ester began to appear. In this way he studied the influence of varying amounts of sodium methylate on the velocity of the reaction, showing that the velocity of the reaction is quite nearly proportional to the amount of alkali used. He adopted Claisen's view as to the mechanism of the reaction. "Without addition of alkali" he "could get absolutely no transformation, even when, to accelerate the reaction, the mixture was boiled two hours under a return condenser." When it is remembered that the mixture, consisting mainly of methyl alcohol, must have boiled at about 65°, this seems rather mild treatment, particularly as he had no test for small amounts of the methyl ester. In an experiment quoted below no crystals of a similar methyl ester were obtained, and hence no reaction detected, after heating for nearly 2 days at an average temperature of 165°. If the reaction velocity doubles for each 10° C., the velocity should be 1000 times as great at 165° as at 65°, hence Pfannl should have boiled his mixture about 2,000 days or over 5 years. It would be expected that the velocity of transformation of esters would be of the same order of magnitude as that of the formation of esters from the acids and alcohols, and it is well known how slow esterifica-

[1] P. Chem. Soc., **21**, 87; through Chem. Centralbl., **1905**, I, 1234.
[2] *Loc. cit.*

tion is at moderate temperatures in the absence of a catalyst. By working from both ends he proved all the reactions reversible, but in all cases he used an enormous excess of the alcohol so as to get practically complete transformation, in one case actually isolating 92 per cent. of the calculated amount of ester. All of the products were carefully identified by physical properties and even by elementary analysis. In the case of methyl benzoate, which was transformed into the propyl ester by 19 molecules of propyl alcohol and 0.1 molecule of sodium propylate, 85 per cent. of the unsaponified ester was isolated as propyl benzoate. He made no attempts in any case to locate the equilibrium point.

Komnenos,[1] who does not refer to any of the above work, observed the transformation of the esters of acetylenetetracarboxylic acid by sodium alcoholates, and in order to determine whether it was due to the presence of $—CH_2—$ groups in which the hydrogen is replaceable by sodium, extended the study to esters of other acids, and finally to those of benzoic acid. He identified the esters obtained very thoroughly by elementary analysis, and by determining densities, melting points, etc., together with molecular weights and saponification equivalents. From 35 grams ethyl benzoate, 5.4 grams of sodium, and more than 180 grams of methyl alcohol he obtained 10 grams of crude ester, the largest portion of which distilled between 187° and 193° and which he considered as the "purest" methyl benzoate, though its density differed by 0.01 from the obsolete value which he quotes from Strohman.[2] The value which Komnenos did find is, however, only about 0.0015 low, which from Table III shows the presence of 3 per cent. of ethyl ester, which is just the amount which should have been present. He suggests that the reaction may proceed according to the mechanism above quoted from Claisen, though he does not seem to have been influenced by Claisen's work.

There are certain pseudoammonium bases which readily react with alcohols to form oxygen ethers, and which just as readily exchange one alcohol radical for another when simply

[1] Monatsh., **31**, 111–122; **31**, 687–693; **32**, 77–88.
[2] J. prakt. Chem., [2] **36**, 4.

warmed in solution in excess of the second alcohol. These reactions are well discussed, with full references to the literature, by Johnson and Guest,[1] who also find that all the ether-thioureas which they have prepared "react with alcohols, on warming, with transposition of the alkyl groups," the reactions being "reversible,

$$R.NHCSNHCH_2OC_2H_5 + CH_3OH \rightleftharpoons R.NHCSNHCH_2OCH_3 + C_2H_5OH,$$

and ... not influenced by the boiling points of the alcohols, or by the size of the alkyl groups involved in the change." It would be of interest to study quantitatively the equilibria involved and to extend this to the mercaptans.

In the present work encroachment on the fields of these workers has been avoided so far as possible and transformations have been affected by sodium alcoholates only far enough to show that the limits so obtained, making certain allowances for complications, are the same as those obtained without catalyst. It is hoped that these workers will continue their investigations and that the analytical methods here developed may prove serviceable to them.

Materials.

The ethyl alcohol used was very pure, about 99.995 per cent., having a density of 0.785108 at 25°, referred to water at the same temperature and reduced to a vacuum.[2]

The methyl alcohol had stood for a long time over anhydrous copper sulphate and was distilled from this. It had a density of 0.80018 (15°/15°). According to Doroszewski and Roshdestwenski[3] this corresponds to 98.623 per cent. of alcohol. Since the water content makes no difference and can be allowed for in the calculations, no attempt was made to dry it further.

The ethyl benzoate was a sample prepared for a previous investigation.[4] It was redistilled, as from long standing it had acquired a faint yellow color. Of this, 257 grams out of

[1] J. Am. Chem. Soc., **32**, 1280.
[2] For this I am indebted to Dr. Robertson of this laboratory.
[3] Chem. Zentralbl., **1910**, I, 155.
[4] This Journal, **43**, 493.

300 distilled between 212°.2 and 212°.3, corrected. Practically all the rest went over within a fraction of a degree, but only the above-mentioned fraction was used in the quantitative work. The density was 1.04475 (25°/25°).

The methyl benzoate was prepared from the above sample of methyl alcohol. The crude ester was well washed with soda solution and then shaken ten times, for ten minutes each time, with more than its own volume of water. It was then dried for two weeks over fused calcium chloride. On distillation, 230 grams out of 313 went over between 198°.8 and 199°.1, most of the remainder going over within a degree. The largest portion boiled at 198°.9 at 753.9 mm. (thermometer stem in the vapor). It had a density of 1.08714 (25°/25°), uncorrected for air displacement.

The ethyl *p*-brombenzoate was prepared from acid melting at 249°.5 (uncor.), or 1°.5 below the best acid. It was well washed and dried by passing hydrogen through it at 100°. On distillation, 16.6 grams of it distilled from 264° to 267°, leaving about 1 gram residue. Of the first fraction, on redistillation, 15 grams went over from 264° to 267°. Nearly all of this went over between 265°.5 and 266°.5 at 768.1 mm., the stem of the thermometer being entirely in the vapor. Errera[1] gives 262° (cor.) at 737 mm. The 264°–267° fraction alone was used in the quantitative work. Its density was 1.43537 (25°/25°), not corrected for air displacement. The Anschütz thermometer used gave the boiling point of acetanilide as 305°, agreeing exactly with Perkin's determination.

The benzyl acetate used was prepared according to the method of Seelig.[2] The crude ester was washed twice with soda solution and twice with water. On distilling, 5 grams went over up to 213°, 133 grams between 213° and 217°, and 9 grams from 217° to 218°, leaving 3 grams of residue. The second fraction was redistilled; 19 grams went over below 214°, and 90 grams from 214° to 216°, leaving 16 grams residue. Most of this 90 grams boiled very close to 215°.3 at

[1] Gazz. chim. ital., **17**, 211.
[2] J. prakt. Chem., [2] **39**, 162.

756.6 mm. An Anschütz thermometer was used and the stem was entirely in the vapor. This boiling point is considerably above 206°, the boiling point given by Conrad and Hodgkinson,[1] but not so much above the 210° to 213° mentioned by Higley.[2] The fraction between 214° and 216° had a density of 1.05462 (25°/25°). Only this was used in the quantitative work.

The ethyl thiolbenzoate was the same sample used in a previous investigation.[3]

The mercaptan was also a part of the preparation previously used.[3]

Preliminary Experiments.

With Hydrochloric Acid as Catalyst.—To 1.200 grams of ethyl *p*-brombenzoate (4.240 millimoles) was added 4.921 grams of methyl alcohol (152 millimoles), and dry hydrochloric acid passed in to the amount of 0.163 gram, or about 3 per cent. of the weight of the alcohol. The mixture was then sealed up and heated in a boiling water bath for 1.5 hours. On cooling the mixture, beautiful white needles separated. No pressure was found when the tube was opened. On evaporation the mixture left 1.1123 grams of white needles, the calculated weight of methyl ester being 1.125 grams. These melted without purification at 68° to 71° and after crystallizing once from methyl alcohol at 78°. The melting point of methyl *p*-brombenzoate is given by Rupe[4] as 81°, by Sudborough[5] as 78°, and by Thiele and Rossner[6] as 79°–80°.

This experiment shows in a clear-cut way that the ester of one alcohol can be transformed into the ester of another alcohol under the influence of hydrochloric acid. That is, ethyl *p*-brombenzoate may be esterified by methyl alcohol, and a methyl ester produced, under exactly the same conditions under which the free acid is esterified. The low melting point of the crude product indicates that a small amount of the ethyl ester remained.

[1] Ann. Chem. (Liebig), **193**, 320.
[2] This Journal, **37**, 311.
[3] *Loc. cit.*
[4] Ber. d. chem. Ges., **28**, 260.
[5] J. Chem. Soc., **67**, 592.
[6] Ann. Chem. (Liebig), **308**, 212.

Without Catalyst.—A mixture of 0.4819 gram ethyl *p*-brombenzoate and 2.1915 grams methyl alcohol was sealed up and heated 24 hours at about 150° and then 20 hours at about 180°. Since, on cooling the mixture below 0°, no crystals were formed, it was further heated for 42 hours at about 208°–215°. This time, on cooling to —20°, an abundance of white needles formed. On remaining a long time at room temperature, the fine needles were transformed into large transparent flat needles. Slight pressure was found on opening the tube. The needles, after simply wiping with filter paper, melted at 78°.4.

This experiment shows that the transformation of an ester of one alcohol into the ester of another alcohol, or the esterification of an ester, takes place, without catalyst, under the same conditions, at something like the same rate as the esterification of the corresponding acid.

The Partition of Benzoic Acid between Ethyl and Methyl Alcohols.

Analytical Method.—Since ethyl benzoate has an apparent density of 1.04475 (25°/25°) and methyl benzoate a density of 1.08712 (25°/25°) the difference in density is 0.04237. Hence, provided there were no contraction or expansion on mixing, 1 part of methyl benzoate added to 424 parts of the ethyl ester would raise the density by one unit in the fourth decimal place, which means that in a mixture of the two a difference of density of 0.0001 corresponds to a difference of 0.23 per cent. in the composition of the mixture. In order to ascertain the change of volume on mixing the two esters, five mixtures of varying proportions were made up and the densities of these taken.

The next question was whether a method of treatment could be found which would certainly free the mixture of esters from benzoic acid, water, ethyl and methyl alcohols without altering the relative proportion of the two esters in the mixture. After taking the densities of the above-mentioned five mixtures, each of which weighed about 12 grams, 4 cc. of ethyl and 2 cc. of methyl alcohol, together with about 0.2 gram benzoic acid, were added to each and then each put

through the following purification process. The mixture was put into a tube about 13 × 320 mm. closed at one end. An approximately equal volume of 2 per cent. sodium bicarbonate solution was added, the tube corked and shaken for ten minutes. The aqueous portion was pipetted off, and the ester mixture further washed three times with at least its own volume of water, the shaking being continued ten minutes each time. After the last washing the mixture was poured into a test tube and as much as possible of the water removed by wiping with damp filter paper. The tube was then placed in a bath of boiling water for one hour, a current of dry hydrogen, issuing from a fine capillary, being passed through the mixture. The density was then taken. In Table III are given in the first line the original molecular percentages, next the weight percentages, then the original density, the difference in density corresponding to 1 molecular per cent. of methyl ester, and lastly the density after the above treatment, and the error in molecular per cent. of methyl ester.

Table III.

	I.	II.	III.	IV.
Mol. per cent. methyl ester	0.00	19.95	38.08	49.00
Wt. per cent. methyl ester	0.00	18.43	35.80	46.55
Density	1.04475	1.05231	1.05949	1.06404
Difference for 1 per cent.	.....	0.000379	0.000396	0.000417
Density found	.....	1.05238	1.05944	1.06414
Error in per cent. of ester	.....	0.14	0.12	0.23

	V.	VI.	VII.
Mol. per cent. methyl ester	68.59	79.14	100.0
Wt. per cent. methyl ester	61.29	77.47	100.0
Density	1.07047	1.07739	1.08714
Difference for 1 per cent.	0.000441	0.000445	0.000467
Density found	1.07037	1.07138	.....
Error in per cent. of ester	0.23	0.02	.....

The densities were taken with pycnometers such as described by Jones and Bingham.[1] A number of these were used, varying in capacity from 8 to 1.3 cc., according to the amount of liquid available. With the larger ones 0.1 mg. difference in the weight of the filled pycnometer corresponds to a difference of 0.00001 in the density while in the smallest the same difference in weight corresponds to 0.0001 in the density. For uniformity all of the densities are carried out to five places of decimals, but little importance is attached to the last figure. In the analyses, in the experiments which follow, the percentages reported were found by interpolation from the above table, the molecular percentage being supposed to increase regularly as the density between the two points determined. Since the curve joining the points is not a straight line, this is not strictly correct, but the error thus made is not great.

The data as to densities of the mixture in the above table are presented in the diagram, Fig. I. Since all the points

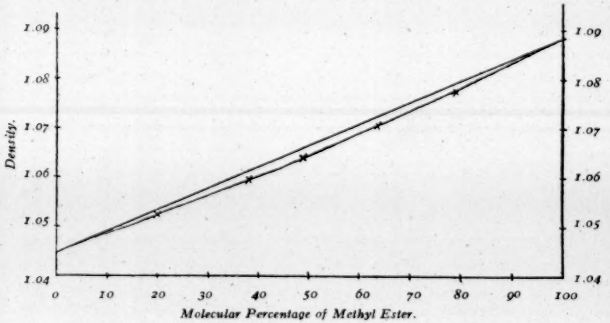


Figure 1.—Densities of Mixtures of Ethyl and Methyl Benzoates.

representing the densities of mixtures lie below the straight line which is drawn joining the densities of the pure esters, the densities of all mixtures are less than the average densi-

[1] This Journal, **34**, 495.

ties of the components, and hence there is expansion on mixing.

All of the densities were taken at 25° and compared with water at the same temperature. No correction was made for air displacement. As the densities are all nearly the same and also not far from that of water this correction would be very small. Before setting, each pycnometer was allowed to remain in a large water bath, the temperature of which seldom varied more than several thousandths of a degree from the mean temperature.[1] On account of the high viscosity of the esters they do not drain properly and a considerable amount of liquid always sticks to the sides of the small bulb in the pycnometer. This is probably much the largest source of error in the determinations. The magnitude of the error due to this was not realized in the first part of the work, but in the latter part this error was minimized by taking care that in filling the pycnometer the liquid was either not drawn into the bulb at all or only a very little of the way in. This was accomplished by putting a Mohr pinchcock on the rubber tube through which air was drawn to cause the liquid to rise in the pycnometer. This was closed when the liquid had risen just a little way above the mark. The pinchcock remained on the pycnometer all the time it was in the bath, and the final setting was made by squeezing the rubber tube between the pycnometer and the pinchcock. Each time, before use, a pycnometer was rinsed out four times with alcohol and dried by warming and aspirating air through it. When taken out of the bath the pycnometers were rinsed off with alcohol, wiped with bibulous paper, and allowed to stand in the balance case for a considerable time, usually a half hour, before weighing.

Experiments with Hydrochloric Acid as Catalyst.—Two mixtures of methyl benzoate and ethyl alcohol and one of ethyl ester and methyl alcohol were made up and dry hydrochloric acid passed in for ten minutes, the mixture being kept at 0°. The mixtures were sealed up and kept at 75°

[1] For the use of this excellently regulated bath I am indebted to the kindness of Associate Professor Acree.

for 3 hours and then at 85° for 8.5 hours. Before being put through the regular process described above, the mixtures were given a preliminary washing with water to remove most of the hydrochloric acid. In all of the reaction mixtures considerable amounts of alkyl chlorides appeared to be present, as gas was given off continuously during the washing. The proportions of the constituents, as well as the results obtained, are given below in Table IV, in which the actual weights are given in the first three lines, and the weights in millimoles in the next three:

Table IV.

	Methyl ester and ethyl alcohol.		Ethyl ester and methyl alcohol.
Weight of ester	11.173	11.145	12.016
Weight of alcohol	4.704	9.597	3.011
Weight of HCl	2.206	2.421	2.214
Ester in millimoles	82.12	81.92	80.06
Alcohol in millimoles	102.15	208.4	92.77
HCl in millimoles	50.52	66.42	62.16
Density of product	1.05980	1.05436	1.06266
Per cent. of methyl ester, found	38.82	25.12	45.69
Per cent. of methyl ester, calculated	47.92	31.04	57.00

Under "calculated" is put the per cent. obtained by multiplying the equivalent amount of methyl, whether originally present in the ester or in the alcohol, by 1.145, the equivalent amount of ethyl present by 1, and calculating the percentages with these two numbers. This is the same as assuming that the benzoyl is partitioned between methoxyl and ethoxyl, when present in equivalent amounts, in the ratio of 2.281 to 1.991. These three experiments confirm the one given above in showing that ester transformation takes place readily in the presence of hydrochloric acid, and further that the reaction proceeds readily from either end, even when large excesses of the alcohols are not used. The percentages of the two esters found do not agree with the calculated equilibrium points, there being in all cases less of the methyl ester than was expected. The deficiency is greatest when there

was least of the methyl alcohol and least when there was the most of that alcohol. This is readily accounted for by supposing that the hydrochloric acid acted to a greater extent on the methyl than on the ethyl alcohol to form alkyl chlorides.

The following experiments were made, using only about one-tenth as large a proportion of hydrochloric acid and a much lower temperature. The samples were made up and sealed up in exactly the same way as the above except that the hydrochloric acid was passed for only 30 seconds and, after sealing, the tubes were put in the 25° thermostat. On account of the smaller amounts of ester mixture a 3-gram pycnometer was used. The last sample remained at 25° for about 71 hours, the other three for 28 days. The results are given in Table V in the usual form:

Table V.

	Ethyl ester and methyl alcohol.		Methyl ester and ethyl alcohol.	
Weight of ester	5.0940	5.0620	5.2432	5.4147
Weight of alcohol	4.0066	1.5793	1.3495	5.0527
Weight of acid	0.1110	0.1148	0.1606	0.1080
Ester in millimoles	33.94	33.73	38.54	39.80
Alcohol in millimoles	124.69	49.15	29.30	109.72
Hydrochloric acid in millimoles	3.045	3.150	4.406	2.963
Density of product	1.07754	1.0	1.06477	1.08090
Per cent. of methyl ester, found	79.59	65.09	50.66	86.42
Per cent. of methyl ester, calculated	80.60	64.92	60.00	29.34

The results here given show the same things as those in Table IV and the deficiency of methyl ester, which is less in this case, may be explained in the same way. The fourth sample, which was heated only 71 hours at 25°, shows something of the rate of the reaction.

With Sodium Alcoholates as Catalysts.—The following eight experiments were made to determine the equilibrium point, using sodium alcoholates to accelerate the reactions. In the

first set of four, for 1 molecule of ester from 0.02 to 0.03 molecule of the alcoholate was used, and in the second set, 0.01 or less. In each experiment the ester and alcohol were successively weighed into a test tube which had previously been drawn down to a narrow neck. A bit of freshly-cut sodium was dipped in alcohol, then in ether, quickly wiped off, and thrown into the tube. As soon as the evolution of hydrogen had ceased the tube was sealed off and weighed. The gain in weight was multiplied by 23/22 to obtain the weight of the sodium. The first four samples remained at room temperature for 14 days and the others for 15 days. Of the first set, the first mixture remained perfectly clear and colorless, while in the second a precipitate began to form soon after adding the sodium and increased in amount during the first day or two till the whole mixture solidified entirely to a pure white, cheesy mass from which not a drop of liquid could be separated even by vigorous shaking. In the third mixture the precipitate soon began to form and continued till it filled much of the solution, but considerable clear liquid remained. The fourth mixture remained clear for quite a time, but finally deposited a small amount of precipitate, a part of which was granular and the rest gelatinous. The precipitates in the last two did not resemble that in the second tube, but were more gelatinous and semitransparent, somewhat like freshly precipitated silicic acid. Both of these turned slightly yellow. Such precipitates have been noticed by Claisen, Higley, Komnenos, and others. The analytical process was identical with that above described except that the mixtures were given a preliminary wash, with only slight shaking, with the sodium bicarbonate solution so as to eliminate the caustic alkali. The results of the first set are given in the usual form in Table VI:

Table VI.

	Ethyl ester and methyl alcohol.		Methyl ester and ethyl alcohol.	
Weight of ester	5.1914	5.3798	5.2788	5.5584
Weight of alcohol	7.1302	1.6945	2.1612	7.8359
Weight of sodium	0.0161	0.0275	0.0282	0.0225
Ester in millimoles	34.59	35.85	38.80	40.85
Alcohol in millimoles	219.68	52.21	46.93	170.16
Sodium in millimoles	0.698	1.193	1.225	0.976
Density found	1.08183	1.07063	1.06421	1.05411
Per cent. of methyl ester, found	88.49	63.95	49.41	24.50
Per cent. of methyl ester, calculated	87.91	62.51	48.74	21.56
Difference	0.58	1.44	0.67	2.94

Of the second set of four experiments, the first mixture remained perfectly clear and colorless, in the second a precipitate formed and took up most of the solution, and in the third after some time a gelatinous precipitate appeared, while in the last there was nothing for quite a while, but finally a partly granular and partly gelatinous precipitate. The third and fourth turned slightly yellow. In the third mixture the ester and alcohol were almost exactly equivalent and the sodium alkylate just 1 per cent. of the alcohol. The results are given in the usual way in Table VII:

Table VII.

	Ethyl ester and methyl alcohol.		Methyl ester and ethyl alcohol.	
Weight of ester	5.3963	5.3251	4.9089	5.2051
Weight of alcohol	3.3777	1.7122	1.6731	3.2184
Weight of sodium	0.0071	0.0085	0.0084	0.0078
Ester in millimoles	35.96	35.48	36.08	38.26
Alcohol in millimoles	104.07	52.75	36.33	69.89
Sodium in millimoles	0.308	0.366	0.363	0.340
Density found	1.07741	1.07083	1.06664	1.05949
Per cent. of methyl ester, found	79.10	64.40	54.89	39.78
Per cent. of methyl ester, calculated	76.82	63.00	53.21	38.53
Difference	2.28	1.40	1.67	1.25

It will be noted that, of these eight experiments, four begin with methyl and four with ethyl ester. In two with each ester a large excess of the alcohol was used so as to transform the major portion of the ester. In the first experiment of the first set over 88 per cent. of the original ethyl ester was transformed into the methyl ester, while in the fourth experiment of the same set, over 78 per cent. of the original methyl ester was transformed into the ethyl ester. In all the experiments excess of the alcohol was used. In case of the methyl alcohol the equivalents given are those of the alcohol actually present, making deduction for the water content of the sample.

It will be seen that the results obtained corroborate the observations of all the workers above quoted in that they prove that the transformations take place readily at ordinary temperatures under the influence of even small amounts of the alcoholates and that all of the reactions are readily reversible. It is seen, however, that the enormous excess of the alcohols, 10 to 30 equivalents to one of ester, which have been commonly used, are by no means essential to demonstrate the fact of transformation, though, of course, if it is desired to make the transformation practically complete, such proportions are required in order to reduce the original ester to a negligible impurity.

The results obtained approximate quite closely the figures calculated on the assumption that the partition of the benzoyl between the methoxyl and ethoxyl is according to the partition factors calculated above, and the general proposition may be regarded as proved for this case and rendered probable for other cases, though the differences between "found" and "calculated" are greater than the probable errors with the 3-gram pycnometer used It is difficult to see how equilibrium can be reached in mixtures apparently so far from homogeneous as these were, but, owing to the smallness of the total amount of sodium present, the precipitates observed in the above described mixtures, though exceedingly bulky in appearance, must in reality have been small in actual amount, and must, at any one time, have involved only a small pro-

portion of the reacting substances. Since the amounts, and hence the ratios, of the free alcohols and free esters are altered by a withdrawal of a portion of each of them to form the intermediate product, if a sensible amount of such intermediate product is formed and remains, the equilibrium may thereby be sensibly altered. From the work of Lobry de Bruyn[1] it appears that if, say 17 molecules of sodium were added to a mixture containing 100 molecules each of methyl and ethyl alcohols, there would result 15 molecules of sodium methylate and 2 molecules of the ethylate, leaving the ratio of the alcohols as 85 : 98, which is considerably different from the original ratio 100 : 100. Hence any catalytic agent which forms complexes with any sensible amounts of the reacting substances may be expected to alter the equilibrium. This is different from the supposition made by Acree[2] that a catalyst may be found which will accelerate the forward reaction according to the mth power and the reverse reaction according to the nth power of its concentration. In their discussions, Stieglitz, Acree and others have always postulated that a small amount of the intermediate product should be formed. It appears, then, that for accurate determinations of equilibria, the use of a catalyst is to be avoided as far as possible.

In the case of the esters of acetylenetetracarboxylic acid, Komnenos[3] found that "it is noteworthy that ethyl replaces methyl more readily than the reverse." This statement, for which he offers no sort of quantitative evidence, is rendered improbable by the present experiments.

It is to be noted that in all eight experiments the proportions of methyl ester found are in excess of the amounts calculated. In case the factor, 1.145, which was used in the above calculations, were too small, an excess of methyl ester should also have been found, but in this case the excess would have been proportional to the amount of methoxyl present. This is not found to be the case. It was thought that the excess of methyl ester might have been only apparent, the

[1] Rec. trav. chim., **18**, 41–71 (1899).
[2] This Journal, **38**, 353.
[3] Monatsh., **31**, 121.

excess of density of about 0.001 being due to small amounts of one or more complex substances formed by the action of the sodium alcoholates on the esters. Such substances were found by Higley[1] under somewhat similar conditions. To test this supposition, about 10 milligrams of sodium was added to a mixture of 5 cc. each of ethyl alcohol and ethyl benzoate. This mixture was sealed up and kept at room temperature for 9 days, when it was put through the usual analytical process. In a 3-gram pycnometer, the resulting ester showed the density of 1.04470 as compared with 1.04475 for the original ester. From this it may be concluded that the excess of density found above was not due to the formation of complex compounds.

Velocity of the Reaction with Sodium Alcoholates.—In order to obtain some idea as to the rate of change, under the influence of these catalysts, the following two experiments were made with methyl benzoate and ethyl alcohol at 25°. The times given are only approximate as, in each case, about five minutes was required for the solution of the sodium and the sealing of the tube, and several minutes more for the weighing, though no great amount of transformation could have taken place during this time, as care was taken not to shake the tube and the light alcohol layer remained quite distinct from the heavy ester on which it floated. On putting into the 25° bath, mixing was effected by shaking and the time counted from this moment. The reaction was stopped by pouring the mixture into the sodium bicarbonate solution acidified with an amount of acid equivalent to the amount of sodium alcoholate present. It appears that in 200 minutes the reaction is practically complete, while in the 20-minute experiment only 78.3 per cent. of the possible transformation had taken place. The data are given in the usual form in Table VIII:

[1] This Journal, **37**, 311.

Table VIII.

Time in minutes	200.0	20.0
Ester in grams	5.5341	5.1936
Alcohol in grams	6.1215	6.5342
Sodium in grams	0.0110	0.0184
Ester in millimoles	40.68	38.17
Alcohol in millimoles	132.93	141.89
Sodium in millimoles	0.476	0.798
Density of product	1.05570	1.05635
Per cent. methyl ester, found	28.45	30.07
Per cent. methyl ester, calculated	25.94	23.55

Assuming, for a rough calculation, that the alcohol remains constant during the reaction, we find that 7.4 per cent. of the ester is transformed per minute by 2.1 per cent. of the sodium ethylate equivalent to the ester present. In the experiment given above in Table V, in which methyl benzoate was transformed by 7.4 per cent. of its own equivalent of hydrochloric acid as a catalyst, 19.22 per cent. of the possible amount of transformation was effected in 71 hours, that is, calculating as before, 0.30 per cent. per hour, or 0.005 per cent. per minute. Then, if in transforming an ester with four equivalents of the alcohol, we use 0.01 equivalent of sodium alcoholate, the reaction would proceed at the rate of 3 per cent. per minute, approximately, while if we use instead 0.01 equivalent of hydrochloric acid, the velocity would be only about 0.0007 per cent. per minute. Thus the sodium alcoholate is something like 4000 times as efficient as the equivalent amount of hydrochloric acid. It is well known that sodium hydroxide saponifies an ester enormously faster than hydrochloric acid. As sodium ethylate cannot exist in the presence of benzoic acid we cannot study the formation of an ester from the acid by its agency. In the case of an amide, like benzamide, which is far weaker as an acid than benzoic acid, if we add a quantity of sodium to the alcoholic solution of the amide, the sodium would be partitioned between the alcohol and the amide and some sodium alcoholate would remain as such, and esterification of the amide should be brought about. To test this, 4.1785 grams, or 34.55

millimoles, of benzamide was sealed up with 6.4609 grams, or 130.32 millimoles, of anhydrous ethyl alcohol to which 0.0632 grams, or 2.75 millimoles, of sodium had been added. This mixture was heated 11 hours at 100°. On opening the tube there was a strong odor of ammonia and on pouring the contents into water a globule of ester separated out. To neutralize this 18.5 cc. more of tenth-normal acid was required than could be accounted for by the sodium ethylate present. The mixture was distilled with steam and the distillate, which contained globules of ester, heated with standard alkali and titrated back. The saponification of the ester yielded acid to neutralize 10.5 cc. tenth-normal alkali. Thus about 3 per cent. of the amide had been esterified. A mixture of about the same amounts of benzamide and alcohol, but without the sodium, was heated in the same bath for the same time but gave no detectable amount of ammonia or of ester. Meta- and paranitrobenzamides, which as acids are far stronger than benzamide, were tried both in methyl and in ethyl alcohols with sodium alcoholates, but no ester could be detected.

Without Catalyst.—In order to reach the equilibrium in reasonable time, this work was done at about 220°. The glass tubes, after being sealed at one end and drawn down to a narrow neck at the other, were well extracted with hot dilute hydrochloric acid before use. After weighing in the desired amounts of esters and alcohols, the tubes were sealed and heated in the steel tube previously described.[1] Four experiments were made, two starting with methyl, and two starting with ethyl ester. The proportions were purposely made as various as possible, two mixtures containing excess of the ester and two, a large excess of the alcohol. The process of analysis was exactly as described above. The first mixture was heated 40 hours, most of the time at 187°. As will be seen below, this failed by a considerable amount to reach the expected equilibrium, hence the other three were heated for a longer time and at a higher temperature. The second was heated 24 hours at 150°, 20 hours at 180°, and 42 hours at 208° to 215°. The third was heated about 57 hours, the temperature

[1] This Journal, **43**, 489.

varying from 209° to 218°. On opening this tube there was a slight pressure. The fourth was heated about 70 hours at from 200° to 210°. All of the reaction mixtures were slightly yellow in color. The results are given in the usual form in Table IX, except that duplicate determinations of the density are given and the percentage calculated for both of them:

Table IX.

	Methyl ester and ethyl alcohol.		Ethyl ester and methyl alcohol.	
Ester in grams	13.085	13.258	11.874	12.730
Alcohol in grams	5.513	3.727	1.787	4.754
Ester in millimoles	96.17	97.45	79.12	84.82
Alcohol in millimoles	119.71	80.93	55.06	146.47
Density (1)	1.06614	1.06800	1.06194	1.07172
Density (2)	.....		1.06805	1.06193	1.07168
Per cent. of methyl ester, found (1)	53.76	57.99	43.95	66.40
Per cent. of methyl ester, found (2)	...	58.10	43.93	66.32
Per cent. of methyl ester, calculated	47.91	57.96	44.34	66.41
Difference	5.85	0.08	0.40	0.04

The first mixture had evidently not reached equilibrium. In the third mixture the per cent. found is rather far from the calculated, but the value found is on the side of the equilibrium from which it was being approached and the error may be due in part to insufficient heating, the time in this case being a little less than in the other two. In the last mixture the water present was 62.3 mg. or 3.35 millimoles. The presence of this water did not influence the partition of the benzoyl between the methoxyl and the ethoxyl. The agreement between the percentages found and those calculated may be regarded as satisfactory.

The Partition of Benzoic Acid between Ethyl Alcohol and Ethyl Mercaptan.

In a former paper[1] the two reactions,

$$(11).\ C_6H_5COOH + HOC_2H_5 \underset{1}{\overset{4}{\rightleftharpoons}} C_6H_5COOC_2H_5 + H_2O,$$

[1] THIS JOURNAL, **43**, 502.

$$(12).\ C_6H_5COOH + HSC_2H_5 \underset{25}{\overset{1}{\rightleftharpoons}} C_6H_5COSC_2H_5 + H_2O,$$

were compared and it was concluded that "alcohol is 100 times as efficient in forming esters as its homologue, mercaptan." This figure, 100, was obtained by dividing 4, the value of the constant k in the first reaction, by 0.04, the value of the constant in the second reaction. Since the partit on factors used in this paper are the square roots of these constants, the partition ratio between alcohol and mercaptan should have been obtained by dividing $\sqrt{4}$, or 2 by $\sqrt{0.04}$, or 0.2, which gives 10. That is, alcohol is just 10 times as efficient as *mercaptan in forming esters*, or in the contest for benzoyl.

The results cited below are regarded as only preliminary, as it is evident that the mixtures were not suffic ently heated, but even they show clearly that alcohol and mercaptan replace each other according to the formulation

$$(13).\ C_6H_5COOC_2H_5 + HSC_2H_5 \underset{10}{\overset{1}{\rightleftharpoons}} C_6H_5COSC_2H_5 + HOC_2H_5,$$

and that the reaction is reversible.

The ethyl benzoate and mercaptan, in the one case, and the ethyl thiolbenzoate and alcohol in the other case, were weighed into small hard glass tubes and heated for about 45 hours to about 220°. The amounts of ester used were about 0.300 gram and the amounts of the alcohol or mercaptan were equivalent to from 1 to 4 times this amount of ester. On opening the tubes no appreciable pressure was found, but lead acetate solution, through which the vapors from the mixtures were passed, showed traces of hydrogen sulphide. The contents of each tube were emptied into a small test tube which was stood in boiling water while a stream of tiny bubbles of dry hydrogen was made to pass through the mixture for about half an hour. The sulphur in the mixture was determined by a modification of the method of Morse and Gray.[1]

The weight of sulphur found in the combustion of a weighed amount of the resulting ester mixture was multiplied by the

[1] This Journal, **35**, 451.

proper factor to obtain the weight of thiol ester in the mixture and the difference assumed to be ethyl benzoate. From these weights the equivalents were calculated in the reaction product. Now if a be the equivalent of thiol, $—SC_2H_5$, whether originally present as $C_6H_5COSC_2H_5$ or as HSC_2H_5, and b be the equivalent of ethoxyl, $—OC_2H_5$, whether present as $C_6H_5COOC_2H_5$ or as HOC_2H_5, then the partition of the benzoyl should be in the ratio a/bx, in which x is the ratio of the partition factor of alcohol to that of mercaptan, and if c and d are the equivalents of thiol and oxygen esters found by analysis, then $a : bx :: c : d$ and $x = ad/bc$.

In Table X are given the values of a, b, c, d and x for the experiments starting with thiol ester and mercaptan and in Table XI those for experiments starting with oxygen ester and mercaptan:

Table X.

a	1.957	1.726	1.420	1.840	2.432	2.118
b	3.946	5.298	5.483	2.443	3.309	3.828
c	0.1649	0.1047	0.0887	0.2766	0.3760	0.2347
d	1.368	1.327	1.092	1.283	1.766	1.181
x	4.11	4.13	3.19	3.50	3.45	2.25

Table XI.

a	3.928	5.123	3.469	3.785	2.879	4.139
b	2.014	2.285	2.622	1.845	1.974	1.676
c	0.0549	0.0737	0.0875	0.1312	0.1386	0.1249
d	0.5837	1.602	2.312	1.443	1.486	1.296
x	20.7	48.8	35.0	22.6	15.6	25.6

It is apparent that equilibrium had not been reached in any of the experiments, but if in both series something like the same proportionate approach towards equilibrium had been made, the value of x to which both series converge might be obtained by putting $x = \sqrt{3.44 \times 28.0}$, in which 3.44 and 28.0 are the average values of x from Tables X and XI, respectively. This gives $x = 9.8$, which is near the value 10 deduced above from the previous work.

The Partition of Benzoyl between Hydroxyl, Ethoxyl and the Amido Group.

The extension of this reasoning to the equilibrium between

ammonium benzoate and benzamide and water is interesting. In the esterification of benzoic acid by alcohol and in the transformation of ammonium benzoate into benzamide and water, as has recently been shown,[1] the limits, and hence the partition factors, are of the same order, the limits being 66.7 and about 75 per cent., respectively, and the factors, 1.991 and 2.

$$(14).\ C_6H_5COOH + HOC_2H_5 \underset{1}{\overset{4}{\rightleftharpoons}} C_6H_5COOC_2H_5 + HOH.$$

$$(15).\quad C_6H_5COOH + NH_3 \underset{1}{\overset{9}{\rightleftharpoons}} C_6H_5CONH_2 + H_2O.$$

It would appear then that alcohol and ammonia would partition benzoyl between them in the ratio of about 2 : 3, that is, that ammonia should transform about 60 per cent. of an equivalent amount of ethyl benzoate into benzamide.

Efforts to test this by heating benzamide with alcohol led to complicated results which have recently been reported upon,[2] but an experiment starting from the other end was more successful, though perhaps not absolutely satisfactory. Ethyl benzoate to the amount of 7.826 grams, or 52.15 millimoles, was saturated with dry ammonia at —20°, sealed up and

$$(16).\ C_6H_5COOC_2H_5 + NH_3 \underset{1}{\overset{170}{\rightleftharpoons}} C_6H_5CONH_2 + HOC_2H_5.$$

heated 14 hours at 200°. On cooling, a small amount of crystals formed. It was reheated for 45 hours more at about 200°, and analyzed by distillation with magnesium hydroxide and then with caustic soda. This gave 15.07 millimoles of benzamide and 0.036 of ammonia. Assuming that equilibrium had been reached and calculating in the usual way, this gives in reaction (16) the forward velocity as 170 times the reverse and the equilibrium constant as 170, then the partition factor is $\sqrt{170}$ or 16. From this it appears that if the ammonia had been present in amount equivalent to the ester,

[1] This Journal, **44**, 76.
[2] *Ibid.*, **45**, 38.

equilibrium would have been reached when 92.88 per cent. of transformation into amide and alcohol had taken place. Putting it in another way, in reaction (16) ammonia shows itself 13 times as active as alcohol, in reaction (14) alcohol appears to be 2 times as active as water, then ammonia should be 26 times as active as water, while in reaction (15) it appears to be only 3 times as active as water in the contest for benzoyl. It is not necessary to seek far for an explanation of the discrepancy. In the mixture represented by reaction (15), part, probably the larger part, of the ammonia is in combination with the acid as ammonium benzoate and it is only the free ammonia that is carrying on the reaction. If we assume that 26 is the true partition factor for the $—NH_2$ as compared with the —OH group in reaction (15), then $26/3 = 8.67$. Since the same fraction of the benzoic acid as of the ammonia is taking part in the reaction, $1/\sqrt{8.67}$ or $1/2.94$, equalling 34 per cent., of the ammonium benzoate, is dissociated into benzoic acid and ammonia at the temperature of the experiment, about 210°. This is not an improbable value.

This gives an explanation of the fact observed by Menschutkin[1] that the limit of amide formation shifts toward the amide end with rise of temperature. Measuring the equilibrium between amides and esters at different temperatures may furnish a clue to the dissociation of the corresponding ammonium salts at different temperatures.

The Partition of an Alcohol between Two Acids.

This has been studied in two cases, and though the results are not much more than preliminary, yet they indicate that, in this case also, transformation proceeds, and partition results on the basis set forth in the introduction.

Acetic and benzoic acids are known to give the same esterification limits with ethyl alcohol. Since, for most of the acids quoted in Table II, with the exception of the chloracetic acids which are exceptional in other ways, the limits are practically identical, the limit, and hence the partition factor, for *p*-brombenzoic acid has for the present been assumed

[1] J. prakt. Chem., [2] **39**, 422.

to be the same as for benzoic acid. According to this, if we heat 25 equivalents of *p*-brombenzoic acid with 100 equivalents of ethyl benzoate, we would expect the resulting ester mixture to contain 25 molecular per cent. of the *p*-brombenzoic ester.

Benzoic Acid and Acetic Acid.—A mixture containing 11.0231 grams of benzoic acid and 13.4856 grams of benzyl acetate, that is, 90.32 millimoles of the acid to 89.85 of the ester, was sealed up and heated 40 hours to about 210°. On opening no pressure was found. The product was shaken out with 60 cc. of water containing 14 grams of sodium carbonate and further treated as were the ethyl and methyl benzoate mixtures above described. Two density determinations in 2.3- and 5.5-gram pycnometers gave 1.09063 and 1.09069, respectively.

To 1.3757 grams, or 6.487 millimoles, of the benzyl benzoate obtained as described below was added 0.9592 gram, or 6.39 millimoles, of benzyl acetate, giving a mixture containing 50.37 molecular per cent. of benzyl benzoate. This had a density of 1.08767. Since in the neighborhood of 50 per cent. the curve representing the relation of density to composition of such mixtures has about the same slope as the straight line joining its extremes (for a verification of this see Figs. I and II), which has a slope of 0.00067 change in density for 1 molecular per cent., this same value may be used in calculating the composition of a mixture having the density above found for the reaction product of the above experiment. Thus it is found that this contained 54.88 per cent. of benzyl benzoate when, according to the assumption made, it should have contained only 50.14 per cent. The error is not surprising when the great differences in properties of the two esters involved are taken into account. The difference in boiling points of the two esters is 111°, rendering a partial fractionation of the mixture during the hydrogen treatment possible. The long treatment of the mixture with sodium carbonate to eliminate the acids is also likely to change its composition somewhat. The experiment indicates, however, that acetic acid is replaced by benzoic acid on approximately

equal terms, or, in other words, that benzyl alcohol is partitioned between acetic acid and benzoic acids in approximately the ratio of 1 : 1.

Benzoic Acid and p-*Brombenzoic Acid.*—In order to determine the relation between density and composition of mixtures of the ethyl esters of these two acids, several such mixtures were made up and their densities determined. The results are given in Table XII and graphically in Fig. II.

Table XII.

Ethyl *p*-brombenzoate in grams	0.9282	1.6061	1.9733	2.4688
Ethyl benzoate in g'ms	1.4843	1.0290	1.2241	0.7142
Ethyl *p*-brombenzoate in millimoles	4.053	7.013	8.616	10.779
Ethyl benzoate in millimoles	9.890	6.856	8.156	4.759
Per cent. of brom ester	38.48	60.95	61.72	77.57
Molecular per cent.	29.07	50.56	51.37	67.80
Density of mixture	1.1671	1.2524	1.2557	1.3245

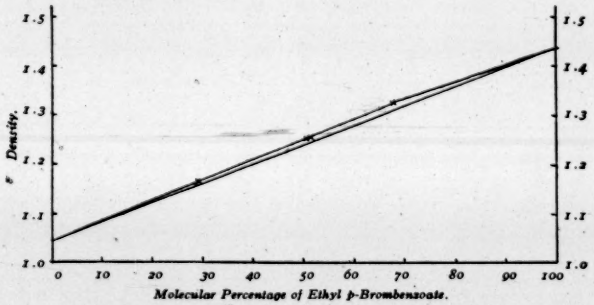


Figure II.—Density of Mixtures of Ethyl Benzoate and *p*-Brombenzoate.

Five experiments were made without any catalyst since the sodium alcoholates are out of the question and, since, in the experiments described above, the hydrochloric acid acted so much on the alcohols to form alkyl chlorides. In the first two experiments benzoic acid and ethyl *p*-brombenzoate

were used, and in the other three *p*-brombenzoic acid and ethyl benzoate. Small samples and small pycnometers, holding 1.3 and 1.6 cc., were employed. The first two mixtures were heated about 40 hours to about 210° and the others 43 hours to about the same temperature. On account of the high melting point of the *p*-brombenzoic acid and its comparatively slight solubility in the ester, except at high temperatures, the acid and ester were mixed by tilting the steel tube, in which the small glass tubes containing the mixtures were heated, after it had reached nearly 200°, several hundred times, so that the liquid would run from one end to the other. On opening, in none of the tubes was more than trifling pressure found. The contents of a tube were washed, with the aid of moderate amounts of ether, into a small separatory funnel and shaken with the calculated amount of a saturated sodium bicarbonate solution for ten minutes. The extraction was repeated with 10 cc. portions of the bicarbonate solution, shaking ten minutes each time, till the aqueous extract failed to give any cloudiness on acidification. The extraction of the acids was complete in three or four operations. The ethereal portion was filtered, concentrated, and the ether and water eliminated by passing a fine stream of dry hydrogen for an hour through the mixture in a test tube surrounded by boiling water. The results are given in the usual form in Table XIII. The percentages were taken graphically from the original drawing for Fig. II.

Table XIII.

	p-Brombenzoic ester and benzoic acid.		Benzoic ester and *p*-brombenzoic acid.		
Ester in grams	4.0118	2.9111	3.1590	2.9591	2.9041
Acid in grams	1.5094	1.7275	1.8272	1.7152	0.6795
Ester in millimoles	17.52	12.71	21.05	19.72	19.35
Acid in millimoles	12.37	14.15	9.090	8.53	3.38
Density	1.2998	1.2706	1.1590	1.1629	1.1044
Brom ester per cent., found	62.[illegible]	55.0	27.8	26.1	14.0
Brom ester per cent., calculated	58.6	47.3	30.2	30.2	14.9
Difference	1.1	3.5	4.8	3.9	2.8

The agreement is only approximate, though in all cases the value found is on the side from which the equilibrium was being approached, which suggests that a part, at least, of the error may be due to insufficient heating. However, the results show plainly that when either of these acids is heated with the ester of the other, there is a partial replacement, the alcohol being partitioned between the two acids approximately in proportion to the concentrations of the two acids.

Double Decomposition between Two Esters.

A mixture was made of 13 cc. each of ethyl benzoate and benzoyl acetate, sealed up and heated about 44 hours to 210°–216°. The resulting mixture was reddish-yellow with some fluorescence. On opening the tube at room temperature some combustible gas escaped. On distilling the mixture, about 0.3 cc. went over below 110°. This had a density less than 1 and the characteristic odor of ethyl acetate. The bulk of the mixture boiled around 209° to 212° and then the thermometer went up rapidly to about 320° (uncorrected). The portion boiling above 240° had a density of 1.0970 and consisted largely of benzyl benzoate. Two other experiments were tried in which the ester mixture was boiled many hours under a return condenser. The products on distillation behaved in the same way as the above. The higher boiling fractions obtained from these reaction products were united and redistilled. The fraction boiling between 300° and 318° (uncorrected) had a density of 1.1116 (25°/25°), while benzyl benzoate is said to have a density of 1.1114 at 16°.

These experiments show that we have double decomposition between two esters.

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BALTIMORE, MD.,
March, 1911.

THE RELATION OF OSMOTIC PRESSURE TO TEMPERATURE.[1]

PART IV.—THE MEMBRANES.

By H. N. Morse, W. W. Holland and C. N. Myers.

A proper investigation of the membranes which are deposited in the interior of cells is impossible, owing to their inaccessibility. The conduct of the material of the membranes towards reagents of various kinds can be studied outside of the cell, but such study yields little of interest or value, so long as the substances whose pressures are under investigation are known to have no chemical action on the membranes. If we overlook, for the present, the destructive attacks upon the membrane by one or more organisms, the whole question of successful or unsuccessful membranes may be truthfully said to turn upon a considerable number of very obscure physical conditions. If a membrane fails, the causes of failure can, in the first instance, only be guessed at, and, ordinarily, they are finally discovered by a wearisome process of exclusion. Some things pertaining to the membranes can be established *a priori*, and others may be learned by microscopic examination of broken cells. But facts which may be brought to light in such ways relate almost solely to the location of the membranes and their attachment to the cell walls.

The first membranes which were formed by the electrolytic process were deposited *within* the cell wall. But it was clear that with a membrane so located it would be impossible to measure osmotic pressure. The obvious objections to such a position are:

1. Every part of a cell wall is filled at all times with some liquid—either water or a solution; hence, if the membrane is *within* the wall, any solution which is placed in the cell for the purpose of measuring its pressure will be diluted or contam-

[1] The work upon osmotic pressure which is in progress in this laboratory is aided by grants from the Carnegie Institution. The earlier papers upon this subject will be found in This Journal, **26**, 80; **28**, 1; **29**, 173; **32**, 93; **34**, 1; **36**, 1 and 39; **37**, 324, 425, and 558; **38**, 175; **39**, 667; **40**, 1, 194, 266 and 325; **41**, 1, 92, and 257; **45**, 91, 237 and 383.

inated by the liquid filling the wall space between itself and the membrane.

2. Even if the space in question, i. e., that between the interior surface of the cell and the membrane *within*, were filled with the solution whose pressure is to be measured, the portion of it which is nearest the membrane would become and *remain* more dilute than the great body of the solution, owing to the slowness of diffusion in the cell wall.

3. It is only in quite porous cells, or rather in cells with quite large pores, that the membrane *is* deposited within the wall, and a membrane so located, being imperfectly supported, always breaks under moderate pressures.

It was the necessity of moving the membrane from the *interior* of the wall, where it was deposited in the cells of the potters, to the *inner surface*, which led to the elaborate experiments in cell making which were described in part in the first of this series of papers. It was there stated that, when the pores are large, the ferrocyanogen ions penetrate far into the cell wall before meeting those of copper, though never quite to the center of it; and that, as the texture becomes finer—in the sense of diminishing diameter of the pores—they penetrate less far, and the membrane is deposited nearer and nearer to the inner surface of the cell wall. When a certain degree of fineness of texture is reached, the membrane is deposited *upon* the surface, and no danger is to be apprehended that the membranes will not be sufficiently supported from the rear.

The texture of a cell, however, may be *too* fine. A microscopic examination of the best of our cells in which membranes have been deposited shows, not only that they *cover* the walls, but that they also *penetrate* to some extent the pores which open on the inner surface—that the membranes are, so to speak, *rooted* into the walls. To this *penetration* of the wall by the membrane we are inclined to ascribe great importance, for it is to this alone, we believe, that the firm adhesion of the membranes to the surface is due. Moreover, it is probably to the absence of such penetration of the pores

by the membrane that the very general failure of membranes made by the diffusion method is to be ascribed.

When a certain degree of fineness of texture is exceeded, the membranes do not adhere well, and it is found, on breaking the cells in such cases, that the penetration of the wall by the membrane is very slight.

There are a number of observations connected with the location of the membrane on the inner surface of the cell and its attachmennt to the wall behind which are worthy of notice in this place. The first of these relates to the distribution of the solvent after it has passed through the membrane into the enclosed solution. It has been maintained that the osmotic pressure cannot be correctly measured without an *active stirring* of the solution; that, otherwise, the entering solvent is not distributed with sufficient rapidity. We confess that we, also, were apprehensive for a long time that it would be necessary, after perfecting the cell, to complicate the work of measuring and to increase its difficulty by the introduction of stirring devices. But, to the best of our judgment at the present time, our fears were without foundation. With the entering water discharging from the free surface of the membrane directly into the solution, currents, caused by differences in density, should be established which would tend to sweep the diluted portions of the solution constantly away from the membrane towards the interior; and we have never observed anything in the conduct of the cells which indicated that these did not suffice to bring about quickly a uniform distribution of the solvent which enters from without. The symptom which would be watched for in this connection would be extreme slowness on the part of the solutions in developing their maximum pressures. But we have had a concentrated solution attain its maximum pressure in less than 24 hours, and maintain it thereafter for several weeks, except for such slight fluctuations as could reasonably be ascribed to *thermometer* and *barometer* effects. The only condition with which we have been able to connect the time consumed in developing the highest pressures is the *thickness* of the membranes.

It has been observed that when—owing to some accident to the regulating devices—there is a considerable and rapid fall in the temperature of the solutions in the cells, it is rarely possible thereafter to secure a successful measurement of pressure. When the temperature of the bath is restored, it is found, as a rule, that the membranes give evidence of having been ruptured during the fall in temperature. It is supposed in such cases—though the explanation cannot be verified—that the membranes have been *detached* from the walls in places.

Whenever a membrane, through long use and frequent mending, has become too thick for prompt action, it is very desirable to replace it by a new and more active one. The operation would seem to be a very simple one, but we have rarely succeeded in performing it successfully. At first, the old membranes were removed with dilute mineral acids; but, having failed to obtain good new membranes in their places, dilute ammonia, ammonium tartrate, and electrolysis in the presence of dilute tartaric acid were resorted to in turn, with indifferent success, however, so far as the character of the new membranes was concerned. The reason for this conduct on the part of cells whose membranes have been removed is obscure. The only tentative explanation which commends itself is that the surfaces of the cell walls, or the mouths of the pores which open upon them, have in some way been modified by the reagents, so that the new membranes do not secure as firm a foothold as they do in new cells. A remedy which has suggested itself is to grind the surface from which the membrane has been removed, but this is always an uncertain operation, because no part of the surface to be removed by grinding can be seen. Another remedy which has been tried with partial success is the rebaking of the cells at high temperatures. This is a practice which was frequently resorted to with the potters' cells, and sometimes with our own, for the purpose of diminishing the size of the pores by shrinkage. In the case of the potters' cells, it was not successful because of the unevenness of the texture. After they had been reburned at the highest practicable temperatures,

some of the pores were still too large to permit the building up of strong membranes. The improvement in this way of cells from which membranes have been removed is limited by the fact that at very high temperatures the glaze volatilizes, and may plug the pores, making it necessary to grind away both the interior and exterior surfaces of the cell.

The process of depositing the membranes has been described in earlier papers, but it will be necessary to restate its main features in order to secure a basis for such comments as we think should be made.

The first step to be taken with the finished cell is to expel the air from the pores and to replace it by water. This has been accomplished from the first by means of "electrical endosmose," that is, by electrolyzing a dilute solution of some salt which nearly fills the cell and in which it is immersed to the lower edge of the glazed portion. The inner electrode serves as cathode, and provision is made for the automatic removal of the water which is drawn through the porous wall into the cell. At intervals the electrolysis is stopped, for the purpose of mixing the liquid which has been removed by the siphon with the liquid in the outer vessel. When it is judged that all the air has been removed from the porous wall, the cell is taken out, emptied and rinsed with pure water. It is then soaked for a time in distilled water, which is frequently renewed. Lastly, it is filled with, and partially immersed in, pure water, and the electrolysis is repeated. When the conductivity, after frequent renewals of the water, has fallen nearly to that which is normal for the distilled water itself, the cell is ready for the deposition of the membrane. If the membrane is not to be deposited immediately, the cell is placed and kept until needed in water in which a little thymol or formaldehyde has been dissolved. The reason for this precaution will appear later when the subject of the *infection* of the membrane is taken up. It is also well to *boil* all the water which comes in contact with the cell, both that which is used in making the solution for the "endosmose," and that which is employed in renewals and in rinsing the cell. Moreover, any further precautions against infection which the pre-

vailing conditions may suggest are by no means superfluous.

The dilute solution which was first employed to sweep the air out of the pores of the cell wall was a 0.005 normal one of potassium sulphate; but, since the slower cations are supposed to carry about with them larger "atmospheres" of water, it was thought that lithium sulphate should give a much larger "endosmose" than the potassium salt. And this was found to be the case. On extending the comparison to several salts with a common anion, the following rule was found to hold good for the substances investigated:[1] "*The quantities of water carried through the porous wall of a cell, under identical conditions, are inversely proportional to the relative velocities of the various cations divided by their respective valencies.*" Since that time, only solutions of lithium sulphate have been used to expel the air from the cell walls.

The arrangement for the deposition of the membrane is as follows: The anode—a copper cylinder—is placed in an empty glass vessel, and within the cylinder is set the cell, which is closed by a rubber stopper carrying the cathode (a platinum cylinder), a funnel with a stem nearly long enough to reach the bottom of the cell and an overflow tube. The circuit is closed, and, as nearly simultaneously as possible, the cell and the vessel outside of it are filled, each with its appropriate solution. The solutions, potassium ferrocyanide and copper sulphate, are of tenth-normal concentration. The voltage which is employed is 110. At first, the resistance is very high, owing to the fact that the cell wall is filled with nearly pure water. Very soon, however, the current begins to increase, and within a short time it attains a maximum. It then drops again steadily for two or three hours and perhaps longer, when a maximum of resistance is reached. If the electrolysis is continued very long after the current has once become constant, the resistance begins to fall again. As soon as the period of decreasing resistance is reached, the cell is removed, rinsed with water, and immersed in a bottle containing a dilute solution of thymol. Here it is allowed to soak from one to three days, with an occasional renewal of

[1] THIS JOURNAL, **36**, 28.

the thymol water, when it is again treated as in the first instance, etc. The resistance rises higher and higher on successive treatments, until a permanent maximum is reached, when the membrane is regarded as ready for its first trial.

The membrane is readily attacked by dilute alkali, hence, during the deposition, the cell is flushed out every two minutes with a fresh solution of potassium ferrocyanide.

The final resistance of the membrane depends both upon the cell and the temperature at which it is deposited. The closer the texture of the cell wall is, the higher will be the resistance at a given temperature, and the lower the temperature is, the higher will be the resistance of the membrane in a given cell.

The cell is placed in a bath of constant temperature for the deposition of the membrane, and usually in one having the temperature at which the cell is afterwards to measure pressure. It has been found that it may be deposited advantageously either *at* or *above*, but not *below*, the temperature at which the cell is to be used. An analogous observation is the fact that, when a cell has been used at one temperature, it is much easier to prepare it to measure at a lower temperature than at a higher one. It is for this reason that we prefer, whenever it is practicable, to measure pressures first at the highest temperature and then at each of the lower temperatures in regular succession.

The copper ferrocyanide membrane has never been known to give a maximum pressure on the first trial. Some of the other membranes which we have under observation, e. g., the ferrocyanide of nickel, seem likely to prove superior to it in this respect. The cell is set up for the first time with a concentrated solution—usually a weight-normal one—and under very little mechanical pressure. That is, the meniscus, when the cell is closed, is left in the lower part of the manometer. The purpose of having it start from this position is to learn as much as possible about the membrane from the conduct of the meniscus while the mercury is being pushed up the tube by the increasing osmotic pressure. If the meniscus rises continuously, without change of form, until the max-

imum pressure is nearly reached, there is reason to believe that a comparatively few repetitions of the membrane-forming process will be required to bring the cell into perfect condition for the measurement of pressure. If, on the other hand, the meniscus rises irregularly, stopping from time to time and changing its form, it can be predicted that two or three, and perhaps four, months will be required to put the membrane in good condition. On the first trial, the solution within the cell is made 0.1 normal with respect to potassium ferrocyanide, and the water in which the cell is placed contains a supposed osmotically equivalent quantity of copper sulphate. The occasional stopping of the meniscus on its way up the tube and the change in its form are believed to be due to a breaking of the membrane, and the resumption of its course is supposed to indicate that the rent has been mended, or at least that the mending process has proceeded so far that the osmotic pressure is increasing more rapidly than the membrane is leaking.

Whatever may have been the conduct of the membrane during the first trial, the cell, after it has been opened and emptied, is thoroughly rinsed with water containing thymol. It is then allowed to soak for two or three days in a closed bottle filled with a dilute solution of thymol, which is frequently renewed. At the close of this period it is resubjected to the membrane-forming process, and later it is set up for a second trial. The quantities of the membrane-formers which are used on the second and subsequent trials depend on the conduct of the membrane during the previous trial. They are reduced as fast as may be until the liquids within and without the cell are 0.01 osmotically normal with respect to the two salts, due allowance being made for their known electrolytic dissociation.

The procedure described above is continued until a perfect membrane is obtained, that is, until the cell is able to maintain for an indefinite period the known *maximum* osmotic pressure of a normal solution of cane sugar. That the cell maintains a *constant* pressure for a long period is not a sufficient test of the membrane; for it often happens that the

pressure remains perfectly constant for a long time—indefinitely, so far as we know—when the pressure observed is not the *maximum* pressure of the solution which was put into the cell. When this occurs, the solution, on opening the cell, is found to have suffered some dilution. The probable explanation is that, at some period, the membrane has broken and permitted some of the solution to escape, and that the rent has afterwards been effectually mended by the membrane formers, so that the observed *constant* pressure is really that of a *diluted* solution—diminished, of course, by the adverse pressure of whatever has escaped from the cell. Right here is one of the most fruitful opportunities for self-deception in the measurement of osmotic pressure, and it cannot be too strongly emphasized that mere *constancy* of pressure is of little value, except when it is proved conclusively at the close of the experiment that the solution has suffered no dilution while in the cell.

The time required to perfect a new membrane varies greatly with different cells. The shortest time in which it can be done is about one month. If, unfortunately, the cell once becomes "infected," three or even four months may be necessary. In some cells it has been found quite impossible to build up a good membrane; but, in such cases, on breaking the cells, defects—usually cracks, the existence of which was previously unsuspected—have been revealed.

A cell which is to be used for the measurement of pressure at a given temperature is maintained at all times at that particular temperature until the work is finished. To this end, no liquids having any other temperature are allowed to come in contact with it, and it is never kept longer than is necessary out of its constant temperature bath.

All solutions of which the osmotic pressures are to be measured are made 0.01 *osmotically* normal with respect to potassium ferrocyanide, the salt being supposed to be completely dissociated at that dilution. The exact quantity of the salt which is dissolved in each 100 grams of water is 83.9 milligrams. The solutions are also made 0.001 normal with respect to thymol, the purpose being to prevent the growth

of *penicillium* in case the solutions or the membranes have become infected.

To each 100 grams of the water in which the cells are placed during a measurement, there are added 123.9 milligrams of crystallized copper sulphate, which quantity is required—if the salt is completely dissociated—to give a 0.01 osmotically weight-normal solution. There is also added enough thymol to make a 0.001 normal solution of that substance. The solutions and the water in which the cells are placed are therefore equally concentrated so far as the thymol is concerned, and they are supposed to contain osmotically equivalent quantities of the membrane-forming salts. Several attempts have been made to ascertain, by means of open manometers, whether the quantities of the two salts which are used are in reality osmotically equivalent; but, owing to complications which will be explained later, it was impossible to arrive at any satisfactory conclusion. The difference between the osmotic pressures of the two, if any exists, is very small.

After finishing an experiment, the cell is emptied, thoroughly washed, and then allowed to soak from two to three days in a dilute solution—usually 0.001 weight-normal—of thymol, which is renewed at least twice a day. It is then ready to be prepared for another measurement of pressure. The preparation consists in subjecting the cell to one or more repetitions of the membrane-forming process, until the high resistance of the membrane indicates that its condition is again satisfactory. An interval of one or two days is usually allowed between any two repetitions of the process for the purpose of soaking the cell in thymol water.

The solution which was removed from the cell at the conclusion of the experiment is compared in the saccharimeter with a reserved portion of the original solution, and if any loss in rotation is detected, the experiment is rejected as unsatisfactory on the ground that the *perfect maintenance of concentration* in the cell contents is the only safe criterion in the measurement of osmotic pressure.

The conduct of a new membrane is very different from that of an old one, especially in respect to the time required

by the solutions to reach the maximum pressures. When the membranes are quite new, the highest pressures are usually reached in less than 24 hours; but as a membrane grows thicker (and probably more dense) in consequence of the frequent and many repetitions of the process of deposition and mending, the cell becomes slower and slower until, after from 12 to 24 months, a solution may consume a whole week in developing its maximum pressure. When this stage in the history of a membrane is reached, the cell is discarded, though it is usually still perfectly fit for the measurement of pressure if given enough time. The principal reason for discarding the "old-timers" is that the labor of preparing a sufficient supply of manometers is too great to permit cells to remain for long periods in the baths.

The following records of two determinations of osmotic pressure will illustrate the difference, as regards the time required for the development of maximum pressure between an excellent new membrane and an old one which, though exceedingly slow, is otherwise in excellent condition for the correct measurement of pressure.

I. New Membrane.

Weight-normal concentration of solution, 0.9. Temperature, 25°. Time of setting up the cell, Jan. 20, 1910, 4.00 P.M.

Date.	Osmotic pressure. Atmospheres.	Date.	Osmotic pressure. Atmospheres.
Jan. 20, 10.00 P.M.	24.127	Jan. 23, 10.00 A.M.	24.102
Jan. 21, 1.00 P.M.	24.148	Jan. 24, 10.00 A.M.	24.125
Jan. 22, 9.00 A.M.	24.120		
		Mean pressure,	24.126

II. Old Membrane.

Weight-normal concentration of solution, 0.6. Temperature, 25°. Time of setting up the cell, Nov. 10, 1910. 4.00 P.M.

Date.	Osmotic pressure. Atmospheres.	Date.	Osmotic pressure. Atmospheres.
Nov. 16, 5.00 P.M.	15.654	Nov. 20, 10.00 A.M.	15.628
Nov. 19, 8.00 P.M.	15.612	Nov. 21, 9.00 A.M.	15.629
		Mean pressure,	15.627

In the case of the new membrane cited above, the maximum pressure was reached in 6 hours; while in that of the old one, 6 full days were required. In one instance on our records, when a very old membrane was used in the experiment, the pressure reached a maximum on the *10th day* and remained constant for 12 days thereafter, when the cell was opened. The measurement was an excellent one, and the only defect of the cell was the excessive slowness with which the water passed through the membrane into the solution.

We have never been able to discover that the concentration of the solution has any influence on the time consumed in developing the final pressure, but it is impossible to make any satisfactory quantitative comparisons for the purpose of answering this question, since no two membranes conduct themselves exactly alike, nor does a given membrane ever conduct itself in precisely the same manner in two consecutive experiments. We are under the impression, however, that the rate at which water will make its way into a solution in any given case is dependent principally on the thickness of the membrane and on the difference between the final and the prevailing pressures. We are also under the impression that the membranes are more active at the higher than at the lower temperatures. But here again, it is impossible to secure any satisfactory quantitative evidence.

The fact that time—and in the case of old cells, a great deal of it— is required for the passage of water through the membranes leads to two very troublesome phenomena in the measurement of osmotic pressure, i. e., to what we have designated, for want of more appropriate names, as *thermometer effects* and *barometer effects*. The first are due primarily to fluctuations in the temperature of the bath, which are followed, of course, by changes in the volume of the solutions. Suppose, after the maximum pressure has been developed in a cell, the temperature of the solution is raised a little above the normal, an increase of pressure results, which should be followed by an immediate discharge of water outward and a slight concentration of the solution. If the discharge were instantaneous, no particular harm would be done; for the

final increase in concentration would be very slight, and the osmotic pressure for the higher temperatures, which is known, would be correctly determined. But the discharge of the necesssary quantity of water is by no means instantaneous. It lasts for hours, and in the case of old membranes, it would continue possibly for days before coming to an end. In the meantime, the gas in the manometer is under the osmotic pressure of the solution plus a mechanical pressure due to the expansion of the solution. If, on the other hand, the temperature falls below the normal, a contraction in the volume of the solution follows, and the gas is under less than the full osmotic pressure until the requisite amount of water has made its way inward through the membrane.

The only remedy for *thermometer effects* is an exact regulation of temperature. But we have never been able to eliminate them entirely, though the fluctuations in the temperatures of the baths rarely exceed 0°.02. The mischief which a falling temperature may make with the correction for meniscus is too obvious to require explanation.

Barometer effects are of an analogous nature. The fluctuations in barometric pressure, according as they are upwards and downwards, are followed by the passage of water inward or outward through the membrane and the correction for atmospheric pressure is, at any given time, very uncertain unless the transference of the solvent is finished. It is for this reason that we have come to dread seasons of highly variable atmospheric pressure.

The highest barometer which has been observed in the course of this work was 785 mm., while the lowest was 735 mm. The difference, 50 mm., amounts to 6.58 per cent. of an atmosphere, which is a relatively large proportion of the osmotic pressure of the more dilute solutions. An error so large as this could not be committed in correcting for atmospheric pressure, but the possible mistakes are considerable during seasons of large and rapid change in the height of the barometer—especially when the membranes in use are old and "slow." The only remedy for *barometer effects* is, of course, the maintenance of constant atmospheric pressure over

the water in which the cell is placed during a measurement, but this is impracticable at present. Some scheme for this purpose will have to be devised, however, when the measurement of the osmotic pressure of very dilute solutions is undertaken.

The evil consequences of the slow passage of the solvent through the membranes, whether *thermometer* or *barometer effects*, are minimized as far as possible in the following ways: (1) Only cells which contain the newest, and consequently the most active, membranes are employed in the measurement of the pressure of the most dilute solutions; (2) the experiments with dilute solutions are undertaken only when the barometer seems likely to remain fairly constant for a considerable period; (3) when the height of the barometer is fluctuating to an unusual extent, the cells are allowed to remain a longer time in the baths; (4) cells in which the membranes have become very slow through long use and repeated mending are discarded, notwithstanding the fact that most of them, except for the *thermometer* and the *barometer effects*, are still efficient.

Thermometer and *barometer effects* can be detected in every record of the measurement of osmotic pressure which we shall present in the later papers. Except for these, the pressure in a cell with a membrane which does not leak, after it has once reached a maximum, should remain perfectly constant as long as the cell is left in the bath. That none of our membranes have leaked is proved by the fact that none of the solutions suffered any loss in rotation. And yet it will be observed, on inspecting the records, that there were, in every instance, slight fluctuations in pressure. They are undoubtedly to be ascribed to the fact that the solvent cannot get through the membranes fast enough to compensate quickly the slight changes in the temperature of the baths and the considerable variations in the pressure of the atmosphere.

It will now be seen why we failed with open manometers to discover with certainty whether our two membrane-formers, in the quantities used, are in reality osmotically equivalent. The difference, if there is any, is smaller than the pos-

sible errors due to *thermometer* and *barometer effects*. To investigate minute differences in osmotic pressure, it will be necessary to have both a perfectly constant bath and a perfectly constant atmospheric pressure.

There is one other point which may be mentioned by way of anticipation in connection with the rate of passage of the solvent through membranes. We have some reason for believing that when the osmotic pressure of electrolytes is studied, it will be necessary to employ *very thick* membranes, and probably membranes of *very small area*. If so, the *thermometer* and *barometer effects* will then be much more formidable than they have been hitherto.

The question as to how long the cells should be kept in the bath, after having once developed what appears to be the maximum pressure, is an important one. We have observed that when a cell once reaches its highest pressure and holds it for 20 hours—with only such fluctuations as can reasonably be ascribed to *thermometer* and *barometer effects*—it may be relied on thereafter to maintain that pressure as long as the cell is left in the bath; or, more definitely, for at least six weeks, since that is the longest time we have had a cell under observation.

In two instances, among the approximately 150 determinations which will be reported, the cells remained in the bath 12 and 13 hours, respectively, after having developed maximum pressure, when they were removed because of accidents to the electrical appliances. In six other instances, the times were 19, 20, 21, 21, 23, and 23 hours. Fifteen remained in the bath 24 hours after reaching the highest pressure, and twenty-five between 25 and 30 hours. Fourteen remained between 30 and 40 hours, and thirty-two between 40 and 50 hours. All the others—about one-third—remained more than 50 hours, and among them three for 4 days, four for 5 days, one for 9 days, one for 11 days and one for 13 days.

It has been the policy to keep the cells in the bath until we were certain from previous experience that no further

change in osmotic pressure was to be expected, and *as much longer* as the current supply of manometers and bath space would permit.

There are appended the daily records of two cells, one of which remained in the bath 13 days and the other 11 days after reaching maximum pressure. Neither solution suffered any loss in rotation. The first is a good example of a comparatively young membrane which is very active, as is proved by the fact that the maximum pressure was reached in less than 24 hours. The second is an equally good example of an old and slow (though by no means decrepit) membrane, as is shown by the fact that it required *8 days* for the development of the maximum pressure. In both cases, the apparent fluctuations in osmotic pressure are confined to the second decimal place, and they are smaller from day to day than were the corresponding fluctuations of the barometer. The *lower* osmotic pressures correspond in general to the *higher* barometric pressures, and *vice versa*. This is characteristic of *barometric effects*. That is, owing to the lag of the water in passing through the membrane, the correction for atmospheric pressure is *too large* when the barometer is *high*, and *too small* when the barometer is *low*.

Table I.

Weight-normal concentration of solution, 0.8. Temperature, 25°. Time of setting up cell, Jan. 4, 1910, 3.00 P.M. Time of first reading, Jan. 5, 1910, 9.00 A.M.

Time.	Pressure. Atms.	Time.	Pressure. Atms.
Jan. 5	21.281	Jan. 12	21.238
Jan. 6	21.253	Jan. 13	21.266
Jan. 7	21.256	Jan. 14	21.257
Jan. 8	21.281	Jan. 15	21.249
Jan. 9	21.280	Jan. 16	21.249
Jan. 10	21.258	Jan. 17	21.246
Jan. 11	21.238	Jan. 18	21.264
		Mean pressure,	21.258

Table II.

Weight-normal concentration of solution, 0.2. Temperature, 20°. Time of setting up cell, Dec. 15, 1910, 12.00 M. Time of first reading, Dec. 23, 1910, 9.00 A.M.

Time.	Pressure. Atms.	Time.	Pressure. Atms.
Dec. 23	5.080	Dec. 29	5.062
Dec. 24	5.086	Dec. 30	5.058
Dec. 25	5.071	Dec. 31	5.035
Dec. 26	5.060	Jan. 1 (1911)	5.033
Dec. 27	5.061	Jan. 2	5.035
Dec. 28	5.077	Jan. 3	5.042
		Mean temperature,	5.058

We come now to a calamity which for four years has delayed, and which continues to delay, the progress of the work more than all other difficulties combined, that is, to the *infection* of the membrane by the fungus *penicillium glaucum*. We are not certain that this is the only species of infection against which we have to contend, but it is certain that the membranes which are attacked by the *penicillium* are quickly ruined, and that they can only be restored by months of painstaking labor. Our first introduction to the pest was described[1] as follows: "*Soon after beginning the measurement of the osmotic pressure of glucose solutions, there appeared upon one of our cells an abundant growth of a fungus which, upon examination, was found to be* penicillium. *Within a few days, it appeared upon one after another of the remainnig cells until all were affected in the same manner as the first. We then exposed several solutions of glucose to the air of the laboratory, and the fungus appeared in all of them in a short time. We had had no similar experience previously, though we had worked with solutions containing invert sugar for more than two years, and the conditions under which we were working were, in general, unfavorable to the fungus. The sudden prevalence of* penicillium *spores in the atmosphere of the laboratory could, however, be accounted for, though it had not been anticipated. At the time, certain changes were in progress in the lower part of the building, which involved the tearing away of old walls, and the*

[1] This Journal, **38**, 34.

atmosphere of all parts of the laboratory was, in consequence, in a somewhat dusty condition."

We have been unable to exterminate the *penicillium*, and we are unable to say precisely how it destroys the membranes, but it is suggested that possibly it finds in the ferrocyanide of copper a supply of nitrogen which it is able to assimilate. It is characteristic of a membrane which has been attacked by the fungus that it can withstand little or no pressure, and always leaks when the cell is set up for the measurement of pressure.

The same paper contains an account of the search which was made for a poison which would kill the fungus without injury to the membranes. Of those tested, two, hydrocyanic acid in gaseous form and thymol, were found to destroy it and to do the membranes no harm. The latter was selected because it is the more easily handled and is the safer of the two.

Since then, every liquid which comes in contact with the cells has been made 0.001 weight-normal with thymol, whether it is the solution whose pressure is to be measured, the water in which a cell is placed during a measurement, or the water in which it is soaked when not in use. The thymol water in which the cells are immersed at all times when they are not otherwise employed is kept in salt bottles which can be tightly closed or in glass jars with closely-fitting covers. More recently, the dry parts of the baths are frequently washed with formaldehyde, and phenol is added to the water in them. Open vessels containing formaldehyde are kept in the constant temperature air spaces above the water baths, and the vapors of it are distributed by means of fans. The rooms in which the baths are located are likewise disinfected from time to time with formaldehyde. Nevertheless, the membranes occasionally become infected. The first evidence of infection is usually the fact that membranes, which were previously rendering satisfactory service, are leaking, and fail to recover readily their fully semipermeable character when resubjected to the membrane-forming process.

The present process of renovation is as follows: The cell

with a membrane which has been injured by *penicillium* (or other organisms) is placed in a *saturated* solution of thymol and allowed to remain for several days. It is then soaked out in the usual—more dilute—thymol solution and subjected to the membrane-forming process. If the membrane shows decided improvement after the first course of treatment, it is repeated again and again until the cell is able to develop the highest pressure and to maintain it for a long period. If the membrane does not respond readily to the treatment just described—that is, if it does not show marked improvement—it is placed under a bell jar with a vessel containing potassium cyanide, and hydrocyanic acid is liberated by introducing dilute acid through a funnel tube having a stopcock. After an exposure of from one to two hours, the cell is removed and soaked out in thymol water, after which it is treated as described above. We have also tried soaking infected cells in dilute solutions of formaldehyde, but we are not yet convinced that such treatment is harmless to the membranes.

The following statement will serve to give an idea of the time and trouble necessary for the renovation of an infected membrane. When the cells which had been in use during the winter and spring of 1909 were put away in June for the summer, all the membranes were in perfect condition. On resuming work the first day of October, it was found that most of the cells were infected. The process of restoration was begun at once and was prosecuted thenceforward without interruption, but it was the middle of January, 1910, before all of the membranes had been again brought to their former sound condition. Profiting by the experience of 1909, the cells were left immersed in a *saturated* solution of thymol during the summer of 1910, and the bottles containing them were sealed up air-tight. The membranes were found to be in excellent condition in October. Unfortunately, however, a number of them were again infected in less than a month.

There is one observation which tends to confirm the idea that the *penicillium feeds* upon the membrane, which would, if correct, explain the ease with which the infection takes place

and the destructive character of it. If a colony of *penicillium* and a quantity of ferrocyanide of copper are added to a solution of sugar, the red-brown ferrocyanide will visibly diminish within a short time and finally disappear, while the *penicillium* increases with great rapidity.

There is another observation which leads us to suspect that our membranes sometimes become infected with other things than *penicillium*. The small quantity of potassium ferrocyanide which is added to the sugar solutions imparts to them a slight but distinct color. In most instances, when the cell is opened, the color in question is found undiminished and unchanged, and the solution which is removed from the cell, after an experiment, cannot be distinguished from a reserved portion of the original solution. However, occasionally— but not often— the solution removed from the cell has a distinct *green* color, and some times a minute quantity of a greenish-blue solid is then found in the bottom of the cell. The phenomenon may recur several times in the same cell, but the course of treatment which is employed for *penicillium* also removes the cause of the green color, whatever it may be. The cells in which the green color appears do not develop the full normal pressure of the original solutions, and the contents of such cells are always found to have suffered some loss in rotation.

JOHNS HOPKINS UNIVERSITY,
March 1, 1911.

OBITUARY.

JULIUS WILHELM BRÜHL.

Prof. Julius Wilhelm Brühl died at Heidelberg February 5th, at the age of 61, having been born at Warsaw, February 13th, 1850. He began his college career at Zurich in 1868 and studied there and at Berlin for 5 years, thence going to Aachen, where he served several years as Landolt's assistant in the Polytechnikum. Here he began the work to which he devoted the greater part of his life, viz., the study of the refractivity of organic compounds. In 1875 he obtained his degree at Göttingen and four years later he was called to the Lemberg Technische Hochschule as professor of chemical technology. The unhealthiness of the climate forced him to

resign his position there in 1884, and after spending some time at Freiburg he went, at Bunsen's solicitation, to Heidelberg as honorary professor at the Hochschule, taking over Bernthsen's private laboratory when the latter entered the employ of the Badische Anilin- und Soda-Fabrik. In 1889 he was lecturing at the University as Bunsen's representative and in 1908 was granted the full title of honorary professor. During this period (1896–1901), Volumes 5 to 9 of Roscoe and Schorlemmer's monumental treatise on organic chemistry were published under Brühl's supervision, with the coöperation of Hjelt and Aschan. His long and painstaking investigations on the relationship between the constitution and refractivity of organic compounds have been of incalculable use in solving problems of constitution which could not be cleared up by other means, and the refractometer is now an indispensible part of the equipment of every organic laboratory, not only where investigations of purely scientific interest are being carried out, but in technical establishments as well.

REVIEWS.

A TEXT-BOOK OF ORGANIC CHEMISTRY. By A. F. HOLLEMAN, PH.D., F. R. A. AMST., Professor Ordinarius in the University of Amsterdam. Edited by A. JAMIESON WALKER, PH.D. (HEIDELBERG), B. A., Head of the Department of Chemistry, Technical College, Derby, England, assisted by OWEN E. MOTT, PH.D. (HEIDELBERG), with the coöperation of the author. Third English edition, partly rewritten. New York: John Wiley and Sons; London: Chapman and Hall, Ltd. 1910. pp. xx + 599. Price, $2.50.

The fact that Professor Holleman's book has gone through four editions in the original Dutch, seven in German, two in Russian, two in Italian, one in Polish and three in English, and that French and Japanese editions are in preparation is sufficient evidence of its popularity. In the preparation of the present from the second English edition, the chapter on the proteins has been rewritten and placed after the sugars, along with the amino acids, and the book has been brought up-to-date by many minor changes and additions and by the deletion of obsolete matter. While the reviewer cannot agree wholly with some of the statements made in the books (as, for example, on page 68, that the esterification of alcohols is a slow reaction because it takes place between molecules), yet, in clearness of presentation and in the judicial use of the more modern physical-chemical ideas as applied to organic chemistry, Prof. Holleman's book ranks among the best we have.

C. A. R.

Die Lösungstheorien in ihrer geschichtlichen Aufeinanderfolge. Von Prof. Dr. P. Walden in Riga. Sammlung chemischer und chemisch-technischer Vorträge. Herausgegeben von Prof. Dr. W. Herz, Breslau. XV. Band, 8/12. Heft. Stuttgart. Verlag von Ferdinand Enke. 1910. pp. 181.

This is one of the most interesting and important books that has appeared in physical chemistry for some time. It is interesting because it is written in the live style which characterizes the publications of Walden, and important because it deals with thoroughness with one of the most important subjects in natural science.

The subject of solution is more wide-reaching and affects more branches of natural science than any other. Chemistry is essentially a science of solutions, and solution is fundamental to the biological sciences in general and to geology. Physical chemistry is connected with so many branches of science largely because it deals fundamentally with the nature of solutions. As the title implies, the whole subject of solution is discussed historically in this book, and sufficiently comprehensively for all practical purposes.

The first two chapters are devoted to the views of the ancients and the third to those held by those living in what may be termed the middle ages of science. The modern theories of solution, including the work of the last century, begin with Chapter IV, and are discussed in this and the remaining six chapters..

The whole discussion is characterized by scientific balance. It, however, seems to the reviewer that rather too much stress is laid upon the views of Pickering, but this is, after all, a matter of opinion.

The value of the work is greatly increased by copious references to the literature. H. C. J.